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THE ATTEMPTED SYNTHESIS OF TWO HEXOSE PHOSPHONATE ESTERS¹

F. C. G. HOSKIN²

ABSTRACT

The synthesis of glucose-1-methylphosphonate and isopropyl glucose-1-methylphosphonate has been attempted. Although the intermediates were successfully prepared, deacetylation failed to give the desired products.

The formation of biologically important phosphate derivatives of lipids, carbohydrates, and other substances is well known. However, it has recently been shown that under circumstances where hexose phosphate esters are enzymatically produced from phosphate, no analogous esters are formed from methylphosphonate (5).

The present report describes the attempted chemical synthesis of barium or potassium glucose-1-methylphosphonate and of isopropyl glucose-1-methylphosphonate. Although intermediates analogous to those encountered in the chemical preparation of glucose-1-phosphate were synthesized without difficulty, neither acid nor alkaline treatment (3, 8) gave the two desired compounds from the corresponding acetylated intermediates. In repeated attempts, white solids were obtained which proved to be either inorganic salts or rather impure glucose.

EXPERIMENTAL

Phenyl Methylphosphonochloridate

Equimolar amounts of phenol and methylphosphonyl dichloride (7) were allowed to react in a manner analogous to that described for the reaction of phenol with phosphorus oxychloride (2). After degassing and the removal of unreacted methylphosphonyl dichloride at about 90° C. (temperature of distillation flask) and 8–10 mm. pressure, the material distilling at 60–80° C. and 0.01–0.02 mm. was collected. A rather large non-volatile fraction probably represented diphenyl methylphosphonate. The crude material was redistilled and, except for a small forerun and residue, was collected at 67–69° C. and 0.01 mm.; $n_D^{27} = 1.5234$; final yield 49%. Calc. for $C_7H_9O_2ClP$: C, 44.12; H, 4.23. Found: C, 43.84; H, 4.52.

Silver Phenyl Methylphosphonate

Phenyl methylphosphonochloridate (80 g., 0.42 mole) was poured over 200 g. ice with shaking. When all of the ice had melted, the cloudy aqueous mixture was extracted several times with ether, the combined ether extracts were back-extracted once with water, and the ether solution was dried with anhydrous magnesium sulphate. After filtration the ether was evaporated and the remaining oily material was dried *in vacuo*

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Contribution from the Suffield Experimental Station, Defence Research Board, Ralston, Alberta.

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at about 65° C. A portion was heated in a distilling apparatus to 200° C. at 0.005 mm. but no distillate was obtained. On cooling, the material showed only slight discoloration but had become quite viscous. Probably a considerable amount of phenyl methylphosphonic anhydride, $(\text{CH}_3\text{P}(\text{O})\text{OC}_6\text{H}_5)_2\text{O}$, had been formed.

The remaining impure phenyl methylphosphonic acid was converted to its silver salt by being heated on a steam bath with an excess of freshly prepared silver oxide suspended in a large volume of hot water. After being heated for 15 minutes, the slurry was filtered hot and the filtrate was evaporated to dryness. Following vacuum desiccation the yield of crude silver phenyl methylphosphonate was nearly quantitative. A hot aqueous solution of this salt was treated with norite, filtered, recrystallized by reduction of the solvent volume and cooling, and was desiccated *in vacuo* over silica gel. Yield was 82% based on phenyl methylphosphonochloridate, allowance being made for the fraction used for the attempted distillation. The silvery white platelets darkened slightly at about 150° C. and melted sharply at 221° C. with decomposition. Calc. for $\text{C}_7\text{H}_5\text{O}_3\text{AgP}$: C, 30.13; H, 2.89. Found: C, 30.34; H, 3.11.

2,3,4,6-Tetraacetylglucose-1-methylphosphonate Phenyl Ester

A total of 9.5–10 g. (approximately 0.035 mole) of silver phenyl methylphosphonate was reacted with 10.0 g. (0.0243 mole) acetobromoglucose (6) according to the directions of Posternak (8) for the reaction of silver diphenyl phosphate and acetobromoglucose. The resulting sirup crystallized readily. The product was recrystallized twice from anhydrous ether – absolute ethanol, treated with norite, and recrystallized once more. The resulting white crystalline powder was readily soluble in ethanol and only slightly soluble in ether or water giving a neutral solution in the latter which yielded no precipitate on addition of silver nitrate. Yield 39%; m.p. 89–93° C. without elevation on subsequent recrystallizations, $[\alpha]_D -7.5^\circ$ (c, 0.4, ethanol–water).^{*} Calc. for $\text{C}_{21}\text{H}_{27}\text{O}_{12}\text{P}$: C, 50.20; H, 5.42. Found: C, 50.15; H, 5.53.

2,3,4,6-Tetraacetylglucose-1-methylphosphonic acid

2,3,4,6-Tetraacetylglucose-1-methylphosphonate phenyl ester (4.2 g., 0.008 mole) was exhaustively hydrogenated in absolute ethanol in the presence of 0.4–0.5 g. platinum oxide catalyst (1). The uptake of hydrogen was complete within the first hour. The alcoholic solution was filtered hot to remove catalyst. The filtrate was cooled and the product crystallized readily. The product, after filtration, was washed several times with anhydrous ether, recrystallized from absolute ethanol, and desiccated *in vacuo* over silica. Yield 87%; needles, m.p. 152° C., $[\alpha]_D -4.7^\circ$ (c, 0.4, water). Calc. for $\text{C}_{15}\text{H}_{23}\text{O}_{12}\text{P}$: C, 42.26; H, 5.44. Found: C, 42.28; H, 5.62.

Silver Isopropyl Methylphosphonate

The silver salt of isopropyl methylphosphonic acid, referred to briefly in a previous publication (4), was synthesized and purified by reactions analogous to those described for the synthesis of silver phenyl methylphosphonate. Isopropyl methylphosphonic acid was collected at 80° C. and 0.008 mm.; $n_D^{25} = 1.4232$. Calc. for $\text{C}_4\text{H}_{11}\text{O}_3\text{P}$: C, 34.78; H, 8.03. Found: C, 34.66; H, 7.95. The silvery white platelets of silver isopropyl methylphosphonate darkened slightly at about 120° C. and melted with decomposition at 210–220° C. Calc. for $\text{C}_4\text{H}_{10}\text{O}_3\text{AgP}$: C, 19.61; H, 4.11. Found: C, 19.62; H, 4.17.

^{*}A small-bore, 4 dm. polarimeter tube was used for this and subsequent determinations.

2,3,4,6-Tetraacetylglucose-1-methylphosphonate Isopropyl Ester

A total of 8.5–9 g. (approximately 0.035 mole) of silver isopropyl methylphosphonate was reacted with 10.0 g. (0.0243 mole) acetobromoglucose. After thorough drying the resulting sirup crystallized with some difficulty on addition of petroleum ether. The product was recrystallized twice from ether–petroleum ether and desiccated *in vacuo* over silica. The fine white crystals were readily soluble in ether, ethanol, or water, giving a neutral solution in the latter which yielded no precipitate on addition of silver nitrate. Yield, 60%; m.p. 73–75° C. Calc. for $C_{18}H_{29}O_{12}P$: C, 46.15; H, 6.24. Found: C, 46.43; H, 6.34. Successive recrystallizations finally gave a product melting at 77–79° C., $[\alpha]_D -4.2^\circ$ (c, 3.1, ethanol–water). Found: C, 46.34; H, 6.56.

Attempted Deacetylation

Repeated attempts to deacetylate 2,3,4,6-tetraacetylglucose-1-methylphosphonic acid with hydrochloric acid in methanol (3) or with dilute sodium hydroxide (8) according to the methods described for the preparation of glucose-1-phosphate led only to inorganic salts which, when subjected to qualitative tests, appeared to be either barium chloride or potassium sulphate, depending on the method employed. Similar attempts to deacetylate 2,3,4,6-tetraacetylglucose-1-methylphosphonate isopropyl ester and to isolate a neutral product yielded a white amorphous substance. Elemental analysis and optical rotation indicated that the product was rather impure glucose.

ACKNOWLEDGMENTS

For the general methods of preparation of methylphosphonic acids and their silver salts from the corresponding methylphosphonohalidates, I have drawn on unpublished results of Mr. A. H. Ford-Moore. Analyses were performed by Mr. Tom Stewart of the Suffield Experimental Station, Ralston, Alberta.

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THE GROWTH OF BUTADIENE POPCORN POLYMER IN THE PRESENCE OF METHYL METHACRYLATE MONOMER¹

GLENN H. MILLER² AND ABOLFATH KHAN BAKHTIAR

ABSTRACT

The rate of growth of butadiene popcorn polymer seed in the presence of methyl methacrylate monomer vapor was found to be logarithmic with time and very sensitive to the presence of hydroquinone in the monomer. The resulting butadiene-methyl methacrylate graft polymer was homogeneous in appearance. No satisfactory kinetic mechanism can be presented at this time.

Butadiene popcorn polymer will propagate itself when placed in the presence of various monomers such as styrene, methyl methacrylate, butyl acrylate, etc. (4, 6). The growths of these graft polymers are known to be rapid, but little attention has been given to the actual rates. A logarithmic rate has been demonstrated for the cases of butadiene popcorn seed in the presence of butadiene (5) and styrene (4) monomers in the vapor phase. The following investigations represent one of several series of experiments designed to determine the generality of this logarithmic growth rate phenomena.

EXPERIMENTAL

The methyl methacrylate was obtained from the Borden Co. Even though all the experiments were carried out in the vapor phase, it was found necessary to remove the 0.06% hydroquinone inhibitor by vacuum distillation of the monomer.

The 11th generation butadiene popcorn polymer seeds used in these experiments were from the same original source as those used in previous experiments and were handled in the manner previously described (3). The average activity of the seeds used varied from 25 to 89%, i.e., the weight per cent increase in 5 days when the seeds were incubated above butadiene monomer at 60°.

The general experimental procedure has been described (4). A weighed amount of butadiene seed was placed on a weighed tuft of glass wool in an 18 mm. O.D. tube above the methyl methacrylate monomer. The monomer was then solidified at dry-ice temperature and the tube evacuated and sealed. Following the desired length of time in the darkness of an oil bath at 60°, plus or minus 0.5°, the tube was opened and the polymer evacuated at room temperature until a constant weight was obtained.

Soluble polymer was extracted from the graft polymer in a Soxhlet extractor. Sintered-glass extraction thimbles were used and the extractions were carried out for 24 hour intervals in an inert atmosphere of nitrogen using benzene as a solvent.

RESULTS

The results of preliminary experiments are presented in Fig. 1, where the final weights of methyl methacrylate-butadiene graft polymers are plotted versus time at 60°. Since the butadiene seeds were placed in the vapor phase it was believed that, owing to its low vapor pressure, the 0.06% hydroquinone contained in the methyl methacrylate would have no effect on the growth of the popcorn. In the case of analogous experiments

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Contribution from the Department of Physical Sciences, University of California, Santa Barbara College, Goleta, California.

²National Research Council Postdoctorate Fellow, 1956-1957.

using styrene (4) the authors found it advantageous to leave the inhibitor in the monomer so that the bulk polymerization would be retarded, thus permitting the growth of the popcorn to be observed for a longer period of time. Curve 2, Fig. 1, however, shows that

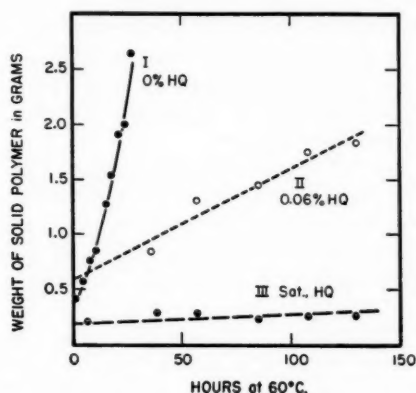


FIG. 1. Effect of hydroquinone on growth of methyl methacrylate-butadiene popcorn polymer.

in the present case inhibited and rather erratic growth occurred when 0.06% hydroquinone was present in the monomer. To further verify the inhibition as being due to hydroquinone, experiments were performed in which the methyl methacrylate was saturated with hydroquinone. The negligible growth rate obtained is shown as curve 3.

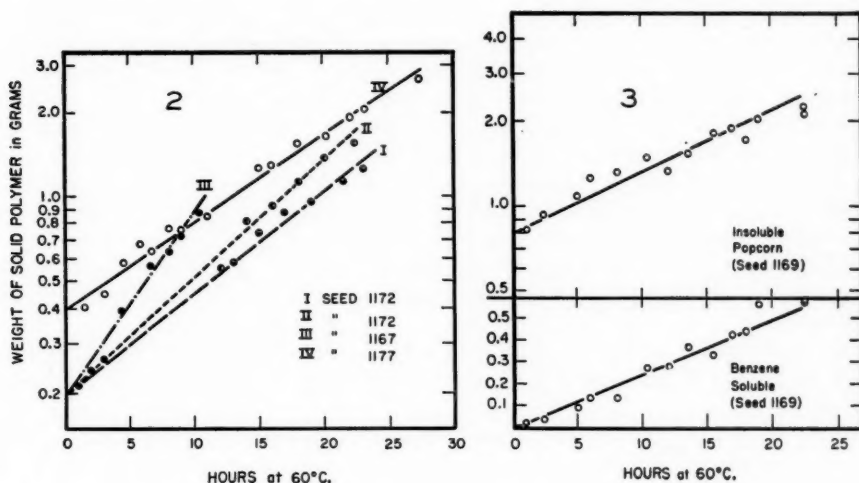


FIG. 2. Growth of butadiene popcorn in the presence of methyl methacrylate vapor.

FIG. 3. Rate of growth of insoluble popcorn and benzene soluble polymer on butadiene popcorn in methyl methacrylate vapor.

Curve 1, Fig. 1, represents the results obtained when no hydroquinone is present in the monomer.

The growth rate of methyl methacrylate - butadiene popcorn graft polymer is shown in Fig. 2. A plot of the growth time in hours at 60° versus the logarithm of the final seed weight in grams was found to be linear. The slopes of the curves varied with the activity of the seed. The rate of popcorn growth in the vapor phase is independent of the amount of methyl methacrylate used as long as some monomer is present. Owing to the bulk polymerization of the monomer, however, the rate of popcorn growth ceases when the vapor pressure of the monomer becomes negligible. For this reason the growth rate could only be followed for less than 30 hours.

Solvent extraction of several samples of graft polymer indicated the presence of various amounts of soluble polymer. In view of this, additional experiments were performed in which larger initial seed samples were used and in which all samples of the resulting solid polymer were extracted with benzene. Fig. 3 shows the linear growth rate observed for the soluble polymer as well as the logarithmic growth of the insoluble popcorn.

The graft polymer was homogeneous in appearance. When samples of the unextracted popcorn were allowed to stand exposed to air they oxidized and became light yellow in color. The color was quite uniform in many samples, but in the majority of cases the portion at the top of the tube did not oxidize as readily as the lower portion where the butadiene seed was initially located, i.e., there was a gradation of color from top to bottom. This variation in oxidation rate can undoubtedly be explained by the presence of the non-popcorn, linear polymer which probably formed to a somewhat greater extent at the top of the sample and thus prevented uniform oxidation. Oxidation of extracted polymer proceeded uniformly in all samples. However, even after 6 months of air exposure small portions of white, non-oxidized masses were uniformly distributed throughout the polymer.

From the curves of Fig. 2 it is apparent that the rate of popcorn growth depends on the initial growth activity of the seed. The difference in slopes observed for curves 2 and 3 can be attributed to variations in initial seed activity, approximately 25% and 37%, respectively, while for curves 1 and 2 (both from the same seed source) the difference is due to variations in monomer purity with regard to the hydroquinone content. The monomer source was redistilled following the collection of curve 1 data and prior to the data of curves 2, 3, and 4. Regardless of these variations, however, the growth rate appears to be proportional to the mass of polymer present at any given time. Within the limits of the experimental method used, no induction period was noted for the growth of the popcorn or for the soluble polymer which formed on the popcorn. These data do not conform to the mechanism of popcorn formation, as previously presented by Devins and Winkler (1).

The results obtained reaffirm the previously published conclusion (2, 3) that the growth of popcorn is not dependent on the decomposition of hydroperoxide linkages on the seed.

Whitby (6) has stated that the extent to which the growth of popcorn polymer will proceed is determined by the extent of unsaturation in the seed polymer. It is difficult, however, to explain why the growth of a monomer being grafted onto an unsaturated seed should not slow down as these centers of unsaturation are utilized. The present work of the authors does not yet warrant a kinetic treatment or theory to explain the growth mechanism.

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ADDITION OF ETHYL RADICALS TO ETHYLENE¹

J. A. PINDER² AND D. J. LE ROY

ABSTRACT

The addition of ethyl radicals to ethylene has been studied in the temperature range 58° to 123° C. The radicals were produced by the mercury photosensitized decomposition of hydrogen in the presence of ethylene, and the rate of the addition reaction was measured in terms of the rate of formation of *n*-hexane by the combination of ethyl and butyl radicals. Corrections were made for the non-uniformity of radical concentrations in the reaction zone. Assuming a negligible activation energy for the combination of two ethyl radicals, the activation energy for the addition reaction is 5.5 kcal. per mole; the steric factor, relative to the square root of the steric factor for ethyl radical combination, is 5.0×10^{-3} .

Although it is generally assumed that the activation energies for the addition of free radicals to olefins are small, relatively few quantitative data are available because of the complexity of the over-all processes and the lack of suitable "reference" reactions. Raal and Danby (7, 8) have studied the addition of methyl radicals to a number of olefins using the photolysis of acetaldehyde as the source of radicals and the abstraction of H atoms from acetaldehyde by methyl radicals as the reference reaction. Mandelcorn and Steacie (6) have used the photolysis of acetone as the source of methyl radicals and the combination of methyl radicals as the reference reaction.

In the present work we have studied the rate of addition of ethyl radicals to ethylene, to form butyl radicals, by measuring the rate of formation of hexane and assuming that this substance is formed exclusively by the combination of ethyl with butyl radicals. The ethyl radicals were produced by the mercury (³P₁) photosensitized decomposition of hydrogen in the presence of ethylene.

It has been established (4) that at temperatures below 200° C. the main features of the reaction can be interpreted in terms of the following mechanism:



At low pressures anomalous variations in the ratio of ethane to butane occur which suggest that under such conditions these compounds are not formed simply by bimolecular reactions of ethyl radicals (1, 9). At the pressures used in the present work these effects are relatively unimportant and the ratio of the rate of formation of ethane to that of butane is in good agreement with the values of k_4/k_3 obtained by other methods (9). As the pressure of ethylene is raised, small but increasing amounts of a product with a molecular weight greater than butane are found. In the present work this product was shown, by gas chromatography, to be *n*-hexane. It was assumed to be formed by the following reactions:



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On the assumption that all butyl radicals formed in [5] disappear by [6] it is evident that the rate of formation of hexane would be given by the expression,

$$d(C_6H_{14})/dt = k_5(C_2H_5)(C_2H_4). \quad [i]$$

Assuming, further, that butane is formed only in reaction [3], it follows that,

$$[d(C_6H_{14})/dt]/[d(C_4H_{10})/dt]^{1/2} = (k_5/k_3^{1/2})(C_2H_4). \quad [ii]$$

The errors which would arise if these two assumptions are not valid will be considered in the Discussion.

Equation [ii] applies to *local* rates. In order to utilize the measured amounts of hexane and butane formed in an experiment to evaluate $k_5/k_3^{1/2}$ it is necessary to apply a correction term which takes into account spatial variations in the ethyl radical concentration throughout the reaction vessel. This correction has been discussed in detail by Cvetanović and Whittle (2); it is of some importance in the present instance because of the large extinction coefficient of mercury vapor.

EXPERIMENTAL

The general procedure was similar to that used previously (3). An improved form of circulating pump was used, having a capacity of approximately $2000 \text{ cm}^3 \text{ min}^{-1}$. Before they entered the reaction vessel the gases were saturated with mercury vapor at 10°C . The quartz reaction vessel was 4.6 cm. in diameter and 11 cm. long; the total volume of the system, including a buffer volume, was 1910 cm^3 .

The ethylene was Phillips Research Grade. Commercial hydrogen was purified as described previously (3). The C_6 hydrocarbons used as reference standards in the chromatography were obtained from the United States Bureau of Standards. The *n*-butane and other gases were supplied by the Ohio Chemical and Manufacturing Company.

The products were analyzed by both low temperature distillation (5) and by gas-liquid partition chromatography using a 7-ft. column containing Octoil-S supported on Celite with helium as the carrier gas. Excellent agreement was obtained between the two methods; the latter served to establish that the C_4 fraction contained only *n*-butane, and that the higher boiling fraction contained only *n*-hexane. With the high ethylene pressures and low conversions used in the present work no other olefins and no odd-numbered paraffins were found.

In order to take account of the spatial variations in the ethyl radical concentration it was necessary to determine the extinction coefficient of mercury vapor for 2537 Å . This quantity is strongly dependent on wave length, even within the narrow range of wave lengths which constitute the resonance "line" emitted by a mercury-rare gas lamp of the type used in the present experiments. As a result, for a given value of the mercury concentration (Hg) the extinction coefficient q depends on the distance L through which the light has passed as well as on the particular lamp used and its operating conditions.

Values of q were obtained in a separate series of experiments using three cells, C_1 , C_2 , and C_3 , having internal path lengths of 0.185, 0.994, and 10.0 cm., respectively. The cells were mounted in a temperature-controlled bath containing distilled water; a parallel beam of light from the lamp entered the bath through a fused quartz window and traversed the three cells. The cross section of the beam was somewhat smaller than that of the cell windows. Each cell was filled with approximately 300 mm. of Phillips Research Grade propane and isolated with a mercury cutoff. Mercury in a side arm on each cell

was allowed to reach its saturation pressure over a period of 16 hours before illumination. The period of illumination was approximately 24 hours. The non-condensable gases were removed with a liquid air trap and the hydrogen formed in each cell was measured. The average decomposition in any one experiment was of the order of 0.1%.

The arrangement of the three cells is shown schematically in Fig. 1. It was necessary to take into account the fraction of light reflected, R , and the fraction transmitted, T , at the windows W_2 and W_3 . Each of these windows consisted of two glass-gas interfaces and two glass-water interfaces. For clarity the incident beam I_0 is shown entering the first cell at an angle to the perpendicular; the various transmitted and reflected beams from which appreciable absorption takes place are indicated. The amount of light transmitted through the rear window of cell C_3 was negligible under the conditions used.

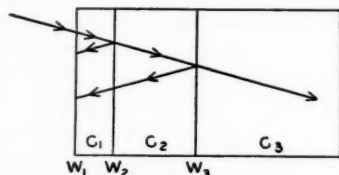


FIG. 1. Arrangement of cells used to determine the extinction coefficient of mercury vapor.

If G_1 , G_2 , and G_3 are the amounts of hydrogen produced in C_1 , C_2 , and C_3 and α_1 and α_2 are the fractions of light transmitted in a single passage through cells C_1 and C_2 it can be shown that

$$1/\alpha_2 - R_3\alpha_2 = 1 - R_3 + T_3G_2/G_3$$

and

$$1/\alpha_1 - \alpha_1(R_2 + T_2^2 R_3\alpha_2^2) = 1 - R_2 - T_2^2 R_3\alpha_2^2 + (1 - \alpha_2 + R_3\alpha_2 + T_3\alpha_2 - R_3\alpha_2^2) T_2G_1/(G_2 + G_3).$$

The values of R and T were calculated from Fresnel's law and the known properties of the window materials. Extinction coefficients were calculated from the expression

$$\alpha = e^{-q(\text{Hg})L}.$$

The mercury concentration was varied from 1.6×10^{-3} to 9.3×10^{-3} mm. by changing the bath temperature. In Fig. 2 the values of q are plotted against L' , the equivalent path length for a saturation temperature of 25°C. A smooth curve can be drawn through the values for α_1 ($L' < 1.0$ cm.) and α_2 ($L' > 1.0$ cm.), indicating that adequate corrections were made for reflection and absorption by the windows.

The kinetic experiments were made with a cell 11 cm. long and a mercury saturating temperature of 10°C.; this corresponds to a path length of less than 3 cm. at 25°C. The value of q used was 15×10^{-15} cm.² molecule⁻¹.

RESULTS

The production of butane and hexane was studied at four temperatures in the range 58.4° to 123.1°C. using a constant hydrogen pressure of approximately 640 mm. (at 22°C.). At each temperature the ethylene pressure was varied by a factor of about 2.5. The effect of hydrogen pressure was also studied. The results are shown in Table I.

The concentrations of hexane and butane are expressed in mm. of mercury in the

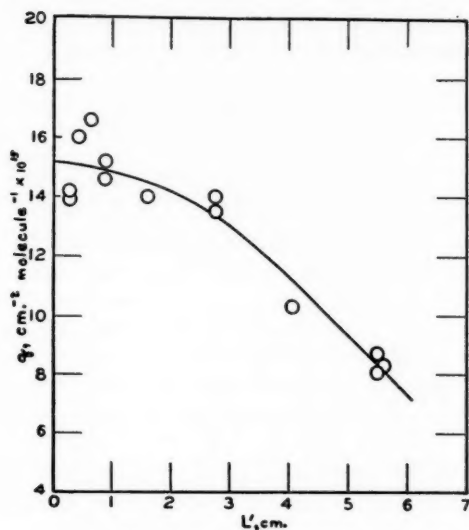


FIG. 2. Dependence of the extinction coefficient of mercury vapor on the equivalent path length for saturation at 25°C.

TABLE I
ADDITION OF ETHYL RADICALS TO ETHYLENE

T, temp., ° K.	t, time, min.	(C ₂ H ₅) _{av.} , mm. at T° K.	(C ₆ H ₁₄), mm. at 22° C.	(C ₄ H ₁₀), mm. at 22° C.	$k_5/k_2^{\frac{1}{2}} \times 10^{12}$ (cm. ³ molecule ⁻¹ sec. ⁻¹) ¹		δ
					Uncorr.	Corr.	
396.3	530	46.74	0.194	0.258	1.093	1.155	1.057
396.3	465	41.24	0.181	0.297	1.172	1.238	1.056
396.3	600	29.25	0.181	0.426	1.214	1.277	1.052
396.3	485	19.54	0.112	0.424	1.237	1.295	1.047
396.3*	480	19.76	0.111	0.420	1.234	1.291	1.046
396.3†	480	19.62	0.111	0.428	1.234	1.291	1.046
374.2	430	48.97	0.138	0.281	0.757	0.804	1.062
374.2	465	39.40	0.135	0.301	0.859	0.910	1.060
374.2	510	29.32	0.113	0.375	0.827	0.873	1.056
374.2	525	19.32	0.0850	0.447	0.855	0.900	1.053
354.9	460	50.38	0.113	0.387	0.471	0.500	1.062
354.9	580	39.61	0.128	0.501	0.532	0.564	1.060
354.9	431	30.20	0.0691	0.402	0.487	0.514	1.056
354.9	550	20.07	0.0728	0.498	0.618	0.652	1.055
331.6	430	48.88	0.0716	0.364	0.307	0.327	1.066
331.6	615	35.64	0.0846	0.647	0.312	0.331	1.061
331.6	555	28.56	0.0577	0.536	0.307	0.325	1.059
331.6	605	20.32	0.0442	0.567	0.308	0.326	1.058

* , † In these two experiments the hydrogen pressure was 215 mm. and 397 mm., respectively; in all of the others it was approximately 640 mm. at 22° C.

system (1910 cm.³) at 22° C.; the concentration of ethylene is the average of the initial and final pressures in the system at the reaction temperature. Using the units given in Table I, the uncorrected values of $k_5/k_3^{1/2}$ given in column six were obtained from the expression

$$k_5/k_3^{1/2} = \frac{7.93 \times 10^{-12} T (C_6H_{14})}{(C_2H_4)_{av.} (C_4H_{10})^{1/2} t^{1/2}} \quad [\text{iii}]$$

In column eight are given the values of the correction term δ by which the uncorrected values of $k_5/k_3^{1/2}$ are multiplied to obtain the corrected values in column seven.

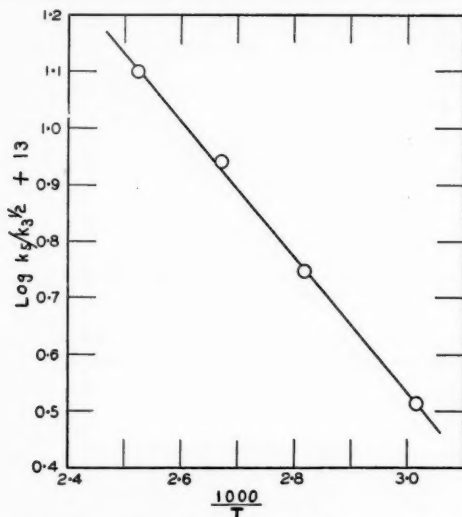


FIG. 3. Arrhenius plot for the addition of ethyl radicals to ethylene.

The quantity δ is a rather complicated function of two parameters, β and s (2). In the present instance these are given by the expressions:

$$\beta = q(\text{Hg})L, \quad [\text{iv}]$$

in which q is the extinction coefficient of mercury vapor to base e , (Hg) is the concentration of mercury vapor in the reaction vessel, and L is the length of the light path (ca. 11 cm.);

$$\text{and} \quad s = \frac{4(k_3 + k_4) q(\text{Hg}) \phi I_0}{k_5^2 (C_2H_4)^2} \quad [\text{v}]$$

On the assumption that $k_4/k_3 = 0.15$ (9), the quantity $(k_3 + k_4)$ in [v] can be equated to $1.15 k_3$. The value of ϕI_0 , the effective incident light intensity in quanta cm.⁻² sec.⁻¹, was calculated on the assumption that the effective number of quanta absorbed per second, $\phi I_0(1 - e^{-\beta})A$, was equal to the number of molecules of hydrogen consumed per second, i.e., to the number of molecules of ethane, butane, and hexane formed per second. The average value of ϕI_0 calculated in this way was 8.2×10^{13} quanta cm.⁻² sec.⁻¹ $\pm 6.5\%$.

An Arrhenius plot of the corrected mean values of $k_5/k_3^{1/2}$ for each temperature is shown in Fig. 3. The least squares value of $E_5 - \frac{1}{2}E_3$ is 5.5 kcal. per mole; the steric factor ratio, $p_5/p_3^{1/2}$, is 5.0×10^{-5} , assuming a mean collision diameter of 4.0 Å.

DISCUSSION

It was considered worth while to evaluate the correction term δ for these experiments because of the uncertainty, arising from the large extinction coefficient, which has been associated with quantitative deductions from mercury photosensitization experiments. It was an obvious advantage, in this regard, to saturate the reagents with mercury vapor at 10° C. rather than at some higher temperature and to use a lamp with a somewhat broadened emission line.

Possible sources of error arise from the assumptions that all butyl radicals are consumed by reaction [6] and that butane is formed exclusively by reaction [3]. If the rate constants were of the same magnitude for the combination of two ethyls, an ethyl and a butyl, and for two butyls, one would expect appreciable amounts of *n*-octane to be formed at the higher ethylene concentrations, particularly at the higher temperatures. There is no evidence for this, in the form of lower values of $k_6/k_3^{1/2}$ under these conditions. It has already been pointed out that no compound of higher molecular weight than hexane was found by gas chromatography. Also, the uncorrected value of $E_5 - \frac{1}{2}E_3$ based on analytical data obtained by gas chromatography differed from the value based on low temperature distillation by less than 0.3 kcal. per mole.

If any of the butyl radicals formed in [5] had undergone disproportionation reactions with ethyl radicals the calculated values of $k_6/k_3^{1/2}$ would be in error.



Assuming that any butene formed in [7] was measured as butane, it can be shown that the right hand side of equation [ii] would have to be multiplied by the term

$$[1 - (R_7 + R_8)/R_B]^{1/2} \cdot R_6/(R_6 + R_7 + R_8),$$

in which R_B is the rate of formation of butane plus that of butene, and R_6 , R_7 , and R_8 are the rates of the corresponding reactions. It can be easily shown that if $R_7 + R_8$ were comparable in magnitude to R_6 the values of $k_6/k_3^{1/2}$ obtained by applying this correction would be strongly dependent on the ethylene pressures, in disagreement with the experimental results. It seems justifiable to conclude that reactions [7] and [8] can be of only minor importance.

There do not appear to be any quantitative data in the literature to compare with the present results on the addition of ethyl radicals with ethylene. However, Mandelcorn and Steacie (6) have discussed their own data and those of other workers on the addition of methyl radicals to ethylene and other unsaturated compounds. They obtained a relative rate constant, $k_{\text{addition}}/(k_{\text{combination}})^{1/2}$, of 11×10^{-12} at 144° C. for the addition of methyl radicals to ethylene. From our data $k_6/k_3^{1/2}$ would be equal to 1.8×10^{-12} at that temperature. Since there is little difference between the rate constant for the combination of two methyl radicals and that for the combination of two ethyls, it is evident that the rate constants for the addition of methyl and ethyl radicals to ethylene do not differ greatly, at least at 144° C. where the results of the three methods used by Mandelcorn and Steacie agree most closely. It is also of interest that the activation energy for the addition of ethyl radicals to ethylene obtained by us falls between the value obtained by Mandelcorn and Steacie (7.0 kcal. per mole) and the corrected value of Raal and Danby (4.6 kcal. per mole) (7, 6) for the addition of methyl radicals to ethylene.

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4-O-METHYL-D-GLUCURONIC ACID AND 4-O-METHYL-D-GLUCOSE¹

P. A. J. GORIN

ABSTRACT

A novel method for the preparation of 4-O-methyl-D-glucuronic acid is described. This sugar and 4-O-methyl-D-glucose were obtained in good yield by two different series of reactions from 2-O-(4-O-methyl-D-glucopyranuronosido)-D-xylose, an acid hydrolysis product of the hemicellulose of *Populus tacamahacca* Mill.

The extension of configurational studies in oligosaccharides to O-methyl-aldobiuronic acids required 4-O-methyl-D-glucuronic acid and 4-O-methyl-D-glucose for synthesis of reference 2-O-glycosyl glycerols. The most ready source of these sugars appeared to be wood hemicellulose which yields 2-O-(4-O-methyl-D-glucopyranuronosido)-D-xylose. However, the hydrolysis of unmodified aldobiuronic acids proceeds only with difficulty and may require 4% acid at 120° C. for 10 to 24 hours for complete scission (15). Under these conditions the free uronic acid monosaccharide is unstable and liable to decarboxylation rendering its over-all yield small. This is true of the hydrolysis of aspen wood hemicellulose to 4-O-methyl-D-glucuronic acid (9). The present paper describes a technique for liberating 4-O-methyl-D-glucuronic acid from the above aldobiuronic acid.

The starting material for the preparation of the expected aldobiuronic acid was *Populus tacamahacca*. Extractive free splinters were acid hydrolyzed by the method of Gorrod and Jones (4) to give a sugar mixture containing the aldobiuronic acid. Fractionation of the hydrolyzate on a charcoal column (14) using ethanol-water mixtures afforded the aldobiuronic acid in good yield. The fact that the compound consumed lead tetraacetate only slowly (2), thus indicating a 1,2-glycosidic linkage, together with subsequent reactions characterized the disaccharide as 2-O-(4-O-methyl-D-glucopyranuronosido)-D-xylose.

Bromine oxidation of the aldobiuronic acid in the presence of calcium benzoate buffer (8) gave the calcium salt of 2-O-(4-O-methyl-D-glucopyranuronosido)-D-xylonic acid (I). The salt of the aldonic acid was treated with two molar equivalents of lead tetraacetate to yield presumably the corresponding L-glycerotriuronic acid derivative (II) since the 4-O-methyl-D-glucuronosido residue is relatively resistant to lead tetraacetate oxidation (11). Hydrolysis of this substance with 10% acetic acid (3) on a steam bath for 3 hours produced the required 4-O-methyl-D-glucuronic acid (III) in 51% yield based on aldobiuronic acid. The material appeared to be free from other sugars on paper chromatograms (10) but was passed through a cellulose column (6) to remove extraneous material. The uronic acid was treated under reflux with methanolic hydrogen chloride and the resulting α,β -methyl-4-O-methyl-D-glucopyranuronoside methyl ester reduced with sodium borohydride (16) to α,β -methyl-4-O-methyl-D-glucopyranoside. Hydrolysis of the glucoside with acid gave the free sugar which was characterized as its crystalline phenylosazone (12). From the above observations it would appear that degradation of an aldobiuronic acid to the component uronic acid is possible, providing it contains a 1,2-glycosidic linkage. This type of reaction has been used previously for the degradation of a neutral oligosaccharide (3). It is noteworthy that disaccharides of most other linkage

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types can be degraded to a suitable 1,2-disaccharide by oxidation of the reducing end with lead tetraacetate (1).

The methyl ester of 2-*O*-(4-*O*-methyl-D-glucopyranuronosido)-D-xylose, obtained by the action of diazomethane on the free acid, was reduced to sirupy 2-*O*-(4-*O*-methyl-D-glucopyranosyl)-D-xylitol. Methanolysis of the disaccharide afforded a mixture of sirupy α,β -methyl-4-*O*-methyl-D-glucopyranoside and xylitol. These two substances were readily separable on a cellulose column, the glucoside being eluted by *n*-butanol and

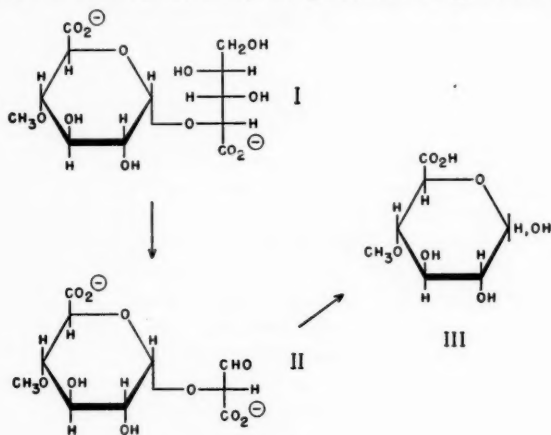


FIG. 1.

characterized after acid hydrolysis by conversion to 4-*O*-methyl-D-glucose phenylosazone. The sirupy xylitol column fraction was warmed with formaldehyde in concentrated hydrochloric acid to yield crystalline 2,4,3,5-di-*O*-methylene-DL-xylitol (5).

EXPERIMENTAL

Paper chromatography was carried out on Whatman No. 1 filter paper using ethyl acetate - acetic acid - water (9:2:2 v/v) as solvent. Melting points are corrected. Evaporations were carried out under reduced pressure at 40° C. Optical rotations were measured at 27° C.

2-*O*-(4-*O*-Methyl-D-glucopyranuronosido)-D-xylose

Extractive free splinters of *P. tacamahacca* (500 g.) were digested in 2 *N* sulphuric acid (4 l.) at 65° C. for 7 days. The mixture was then filtered and the filtrate neutralized with barium hydroxide followed by barium carbonate. After filtration the solution was treated with Amberlite IR-120 and the sugar mixture then fractionated on a charcoal column. Water eluted the monosaccharides and 10% ethanol eluted the aldobiuronic acid together with traces of xylobiose and xylotriose detected chromatographically on paper using the *p*-anisidine hydrochloride spray (7). The solution which contained the aldobiuronic acid was evaporated to a sirup (8.9 g.) having $[\alpha]_D +88^\circ$ (c , 2.3, water).

2-*O*-(4-*O*-Methyl-D-glucopyranuronosido)-D-xylonic Acid (Calcium Salt)

The aldobiuronic acid (3.0 g.) in water (60 ml.) containing calcium benzoate (3.4 g.) was oxidized with bromine (0.90 ml.) for 2 days. Excess bromine was then removed by aeration, the solution filtered, and the filtrate treated with Amberlite IR-120. Benzoic

acid was removed by extracting the solution three times with equal volumes of chloroform. The aqueous portion was treated with calcium carbonate (4.0 g.) and heated at 100° C. for 14 hours. The solution was filtered and added to methanol and a precipitate of the required calcium salt of the aldonic acid was formed. Yield 2.9 g.

4-O-Methyl-D-glucuronic Acid

The calcium salt (1.65 g.) was dissolved in water (8 ml.) and added to acetic acid (175 ml.). Lead tetraacetate (3.7 g.; 2 molar equivalents) was added with stirring and after 18 hours the mixture was treated with 10% oxalic acid in acetic acid (8.2 ml.). Water (300 ml.) was added to the suspension, the solution filtered, and the filtrate treated with Amberlite IR-120. The solution was evaporated to a sirup which was then dissolved in water (90 ml.) containing acetic acid (10 ml.) and was heated at 100° C. for 3 hours. The hydrolyzate was evaporated to a sirup (1.07 g.) which produced on a paper chromatogram a bright red spot, with a rate of 0.9 compared to rhamnose, with the *p*-anisidine hydrochloride spray and a brown spot in the same position using the silver nitrate - sodium hydroxide - acetone dip (13).

The sirup was put on to a cellulose column which was developed with ethyl acetate-acetic acid - water (9:2:1 v/v). The required 4-*O*-methyl-D-glucuronic acid (0.63 g.) with $[\alpha]_D +48^\circ$ (*c*, 1.3, water) was eluted. Yield, based on aldobiuronic acid, 51%.

4-O-Methyl-D-glucose Phenyllosazone from 4-O-Methyl-D-glucuronic Acid

4-*O*-Methyl-D-glucuronic acid (0.62 g.) was heated under reflux for 1 hour in 5% methanolic hydrogen chloride (10 ml.), the solution cooled, neutralized (silver carbonate), filtered, and evaporated to sirupy α,β -methyl-4-*O*-methyl-D-glucopyranuronoside methyl ester (0.45 g.).

A portion of the ester (0.22 g.) in water (10 ml.) was treated with sodium borohydride (0.10 g.) in water (5 ml.). After 16 hours the solution was treated with acetic acid and then shaken with Amberlite IR-120. It was then evaporated to dryness and dissolved in methanol which was boiled off to remove boric acid. This process was repeated three times and the resulting sirup was treated with Amberlite IR-4B in aqueous solution to remove any α,β -methyl-4-*O*-methyl-D-glucopyranuronoside. Evaporation of the solution yielded sirupy α,β -methyl-4-*O*-methyl-D-glucopyranoside (0.17 g.).

The glucoside was hydrolyzed in *N* sulphuric acid (5 ml.) at 100° C. for 18 hours, and the solution was neutralized (barium carbonate), filtered, and evaporated to a sirup (148 mg.) with $[\alpha]_D +61^\circ$ (*c*, 0.7, water). The 4-*O*-methyl-D-glucose thus formed corresponded on a paper chromatogram to the authentic material using the *p*-anisidine hydrochloride spray.

The aldose (0.14 g.) was heated for 2 hours at 100° C. in water (20 ml.) containing phenylhydrazine (0.40 ml.) and acetic acid (1 ml.). The precipitate which formed on cooling was recrystallized twice from benzene to give yellow needles (21 mg.) with m.p. 154-157° C. and $[\alpha]_D +30^\circ \rightarrow 0^\circ$ (constant value) (*c*, 0.5, EtOH). Calculated for $C_{19}H_{24}O_4N_4$: $-\text{OCH}_3$, 8.3%. Found: $-\text{OCH}_3$, 8.3%.

2-O-(4-O-Methyl-D-glucopyranosyl)-D-xylitol

2-*O*-(4-*O*-Methyl-D-glucopyranuronosido)-D-xylose (2.55 g.) in methanol (200 ml.) was neutralized with ethereal diazomethane. The solution was evaporated to a sirup which was dissolved in water (100 ml.) and added to sodium borohydride (1.5 g.) in water (10 ml.). The reaction mixture was left for 16 hours and then worked up by the method

described previously. The product was a sirup (2.32 g.) with $[\alpha]_D +86^\circ$ (c , 0.8 in 50% ethanol).

4-O-Methyl-D-glucose

The 2-*O*-(4-*O*-methyl-D-glucopyranosyl)-D-xylitol (1.92 g.) was heated under reflux in 5% methanolic hydrogen chloride (20 ml.) for 10 hours. The hydrolyzate was then neutralized (silver oxide), filtered, and evaporated to a sirup (1.88 g.). This was fractionated on a cellulose column. *n*-Butanol eluted sirupy methyl 4-*O*-methyl-D-glucopyranoside (0.71 g.) and *n*-butanol half saturated with water eluted sirupy xylitol (0.55 g.).

The xylitol was characterized as its 2,4-3,5-di-*O*-methylene derivative (5), m.p. and mixed m.p. 199–200° C. Calculated for $C_7H_{11}O_5$: C, 47.72%; H, 6.87%. Found: C, 47.95%; H, 6.84%.

Methyl-4-*O*-methyl-D-glucopyranoside (0.24 g.) was hydrolyzed as described previously to 4-*O*-methyl-D-glucose (0.22 g.) with $[\alpha]_D +58^\circ$ (c , 0.8 in water). The sirupy product (0.11 g.) was converted to 4-*O*-methyl-D-glucose phenylosazone (27 mg.) with m.p. 154–156° C. and $[\alpha]_D +30^\circ \rightarrow 0^\circ$ (constant value) (c , 0.5 in EtOH). Calculated for $C_{19}H_{24}O_4N_4$: $-\text{OCH}_3$, 8.3%. Found: $-\text{OCH}_3$, 8.3%.

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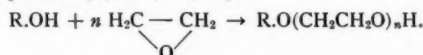
PREPARATION OF SOME PURE POLYOXYETHYLENEGLYCOL ETHERS. PART I¹

B. A. GINGRAS AND C. H. BAYLEY

ABSTRACT

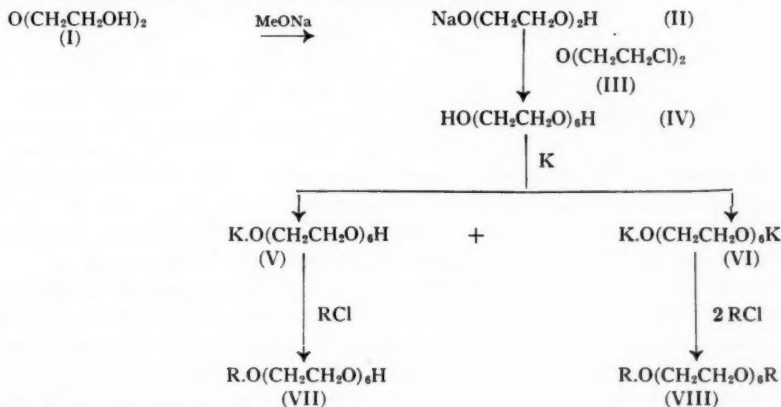
The Williamson ether synthesis has been applied to the preparation of polyoxyethylene-glycol mono- and di-ethers. These were obtained by reacting the mixed potassium salts of hexaoxyethyleneglycol with alkyl or aryl halides. Hexaoxyethyleneglycol monoethers of the type $R.O(CH_2CH_2O)_6H$, ($R = n-C_{10}H_{21}$, $n-C_{12}H_{25}$, $n-C_{14}H_{29}$, and *p*-*iso*- $C_8H_{17}.C_6H_4.O.CH_2CH_2$) and diethers of the type $R.O(CH_2CH_2O)_6.R$, ($R = n-C_{10}H_{21}$, $n-C_{12}H_{25}$, and $n-C_{14}H_{29}$) have been prepared in pure state and some of their properties determined.

Polyoxyethyleneglycol ethers of the type $R.O(CH_2CH_2O)_nH$ ($R = H$, alkyl, or aryl) are usually prepared by polymerization reactions of ethylene oxide with itself or with the appropriate alcohol or phenol (2, 5, 9, 11, 13),



The polymerization is carried out at relatively high temperature and is catalyzed by alkalies. It has been shown that the reaction is a random one, giving a mixture of closely related materials in which the number of molecules of varying sizes is represented by Poisson's distribution formula (3). The separation of such polymeric mixtures into pure constituents is not as yet feasible. Mayhew and Hyatt (7) report two experiments in which two polyoxyethylated alkyl phenols were distilled separately, using a molecular still, and fractions of various molecular weights were obtained in each case. They point out that it would be extremely difficult to isolate a single molecular species by this method.

In an attempt to prepare certain of these ethers in a pure state for other work, use has been made of a direct method of synthesis which has been found to give chemically pure products in satisfactory yields. The method is similar to that used by Hibbert and co-workers (4, 10) for the preparation of the higher polyoxyethylene glycols. It involves the preparation of hexaoxyethyleneglycol monopotassium salt (V) and its subsequent reaction with an alkyl halide as illustrated in the following scheme:

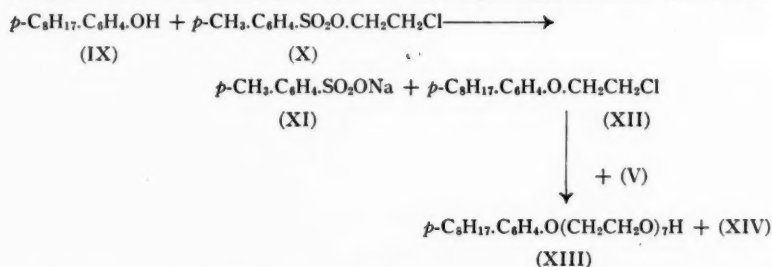


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The reaction of diethyleneglycol (I) with sodium methylate gives the monosodium salt (II). Addition of *bis*(2-chloroethyl) ether (III) to (II) yields hexaoxyethyleneglycol (IV), which reacts with metallic potassium to give a mixture of the mono- (V) and the di-potassium (VI) salts. These, with an alkyl halide, give hexaoxyethyleneglycol monoalkyl ether (VII) and diether (VIII) respectively. In this way, hexaoxyethyleneglycol monoethers ($R = n\text{-C}_{10}\text{H}_{21}$, $n\text{-C}_{12}\text{H}_{25}$, $n\text{-C}_{14}\text{H}_{29}$, and $p\text{-iso-C}_8\text{H}_{17}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{CH}_2\text{CH}_2$) and diethers ($R = n\text{-C}_{10}\text{H}_{21}$, $n\text{-C}_{12}\text{H}_{25}$, and $n\text{-C}_{14}\text{H}_{29}$) have been prepared.

In preparing the *isooctylphenyl* ether sought, i.e., *p*-(1,1,3,3-tetramethylbutyl)phenyl, *p-isooctylphenyl* chloride could not be used as starting material, since the chlorine atom, when attached directly to the benzene ring, does not react under the conditions employed. Hence use was made instead of *p-isooctylphenyl-β-chloroethyl* ether (XII) prepared by the method of Clemo and Perkin (1) for introducing the chloroethyl group into phenols, alcohols, and amino compounds. This method comprises reacting *β-chloroethyltoluene-p-sulphonate* (X) with the appropriate phenol in the presence of alkali, the main products being the *β-chloroethyl* derivative of the phenol and sodium *p-toluene sulphonate* (XI). In the present instance *p-isooctylphenol* (IX) was used and *p-isooctylphenyl-β-chloroethyl* ether (XII) was obtained. This chloroether (XII) was then reacted with the monopotassium salt of hexaoxyethyleneglycol (V), and there were obtained heptaoxyethyleneglycol mono-*p-isooctylphenyl* ether (XIII), and a product (XIV) which is believed to have been formed by a Wurtz-type reaction between two molecules of the chloroether (XII) and potassium and is not as yet positively identified. In this case, the reaction proceeded somewhat differently, since the expected *bis-p*-(1,1,3,3-tetramethylbutyl)phenyl octaoxyethyleneglycol ether (XV) was not formed.



The results of elementary analysis of compound (XIV) are in conformity with the following structure, $p\text{-C}_8\text{H}_{17}\cdot\text{C}_6\text{H}_4\cdot\text{O}(\text{CH}_2)_4\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{C}_8\text{H}_{17}\text{-}p$. Infrared spectra provide further evidence in support of this structure, showing the absence of free hydroxyl groups, the presence of aromatic groups at 6.2μ , and a strong band at 12.2μ indicative of a *p*-substituted phenyl ring. There are no aliphatic ether bands in the 9μ region but two bands at 8 and 9.6μ indicate aromatic ether groups.

The polyoxyethyleneglycol ethers prepared have not been previously reported in the literature and are listed, together with their properties, in Tables I and II.

The monoethers listed in Table I are liquids at room temperature or low-melting solids. They are all soluble in water and, like the corresponding products prepared by polymerization, their solubility decreases with increasing temperature, i.e., they have a "cloud point", which is the temperature at which a dilute aqueous solution becomes turbid. The free hydroxyl group reacts normally with the usual alcohol reagents, and several attempts have been made to prepare solid derivatives, but all were liquids. It

TABLE I
 HEXAOXYETHYLENEGLYCOL MONOETHERS: $R.O(CH_2CH_2O)_6H$

R	B.p. (° C. at mm. Hg)	M.p. (° C.)	Cloud point (° C.)	Analysis	
				Found (%)	Calc. (%) for:
					$C_{22}H_{46}O_7$
<i>n</i> -C ₁₀ H ₂₁ —	200/0.02	14	57	C, 62.31 H, 11.09	62.55 10.90
					$C_{24}H_{50}O_7$
<i>n</i> -C ₁₂ H ₂₅ —	216/0.015	28	55	C, 63.95 H, 11.12	64.00 11.11
					$C_{26}H_{54}O_7$
<i>n</i> -C ₁₄ H ₂₉ —	206/0.02	35	45	C, 65.24 H, 11.39	65.27 11.29
					$C_{28}H_{58}O_8$
<i>p</i> - <i>iso</i> -C ₈ H ₁₇ — C ₆ H ₄ —OCH ₂ CH ₂ —	150/0.01	—	27	C, 65.47 H, 9.79	65.36 9.73

 TABLE II
 HEXAOXYETHYLENEGLYCOL DIETHERS: $R.O(CH_2CH_2O)_6R$

R	M.p. (° C.)	Analysis	
		Found (%)	Calc. (%) for:
			$C_{22}H_{46}O_7$
<i>n</i> -C ₁₀ H ₂₁ —	30	C, 68.70 H, 11.92	68.40 11.70
			$C_{26}H_{54}O_7$
<i>n</i> -C ₁₂ H ₂₅ —	33.5	C, 69.72 H, 12.13	69.90 11.97
			$C_{40}H_{82}O_7$
<i>n</i> -C ₁₄ H ₂₉ —	43	C, 71.08 H, 12.06	71.21 12.16

is of interest to note that trityl chloride, which has been used to prepare solid derivatives of several glycol ethers (12), gave products that were liquids at room temperature.

Infrared spectra confirm the assigned structures for these ethers, showing the characteristic stretching frequencies of the hydroxyl group in the 3μ region, a broad band in the 9μ region indicative of aliphatic ether, and a medium band at 13.9μ due to $—CH_2—$ deformation frequencies in an aliphatic long chain. The spectrum of hepta-oxyethylene-glycol mono-*p*-isooctylphenyl ether (XIII) shows, besides the already mentioned absorptions, the characteristic C=C stretching of the aromatic nucleus at 6.25μ and strong absorptions at 12.1μ , indicative of a *p*-substituted phenyl ring, and at 7.30μ owing to the deformation frequencies of the CH_3 in *t*-butyl groups from the isooctyl chain.

The trityl ethers have infrared spectra similar to those of the free alcohols, but they also show the typical bands due to the aromatic rings and a particularly strong absorption at $14.25\ \mu$ indicative of monosubstituted phenyl rings. They showed no bands in the OH ($3\ \mu$) region.

The dialkyl ethers listed in Table II are not soluble in water. Their behavior resembles that of aliphatic hydrocarbons, and they are soluble in all the hydrocarbon and most usual organic solvents. Their infrared spectra are also of requisite character, being very similar to those of the corresponding monoalkyl ethers except in the $3\ \mu$ region where they show no hydroxyl group bands.

EXPERIMENTAL

Hexaoxyethyleneglycol was prepared according to the method of Hibbert and co-workers (4). An atmosphere of dry nitrogen was maintained in the reaction vessel during the formation of the metallic salts of the glycol and their condensation with the halides. The fractional distillations were carried out with a Vigreux-type column (20 cm. \times 1 cm.). In the case of the trityl derivatives, where quantities less than 1 gram were used, distillations were made in a Späth tube. The solid products were recrystallized to constant melting points, which were taken with a Fisher-John apparatus, and are corrected.

Preparation of Hexaoxyethyleneglycol Monodecyl and Didecyl Ethers

Hexaoxyethyleneglycol (94 g., 0.33 M.) was covered with a layer of petroleum ether (b.p. $60-75^\circ$) and 12.9 g. (0.33 g-atom) of metallic potassium was added in small portions. After 15 hours' stirring, the temperature was raised slowly to 135° while the salt formation was completed. Then, *n*-decyl chloride (69.6 g., 0.39 M.), η_D^{20} (found) 1.4380, η_D^{20} (reported in literature) 1.43799 (6), was added dropwise with stirring over a 2 hour period, the stirring being continued for a further 3 hours at the same temperature. The mixture was then neutral to litmus. The potassium chloride was removed by filtration and the residue distilled under reduced pressure to give two volatile fractions *A* and *B* and a residue *C*.

Fraction *A* was the unreacted *n*-decyl chloride (25 g., b.p. 88° at 1.3 mm. Hg). Fraction *B* was the recovered hexaoxyethyleneglycol (40 g., b.p. 160° C. at 0.01 mm. Hg). The dark brown residue weighed 62.8 g. A sample (9.67 g.) was chromatographed through a column of silica gel. A mixture of ethyl ether and methyl alcohol (19:1) eluted an oily material which, after another purification by the same process, gave crystals of hexaoxyethyleneglycol didecyl ether (VII, $R = n-C_{10}H_{21}$). Ethyl ether and methyl alcohol (2:1) eluted hexaoxyethyleneglycol monodecyl ether, which could not be crystallized. Successive chromatographic separations gave a total yield of 15.35 g. (8%) of the diether and 44.6 g. (31%) of the monoether.

The monodecyl ether (3.03 g., 0.7 M.) and triphenylchloromethane (1.97 g., 0.7 M.) were dissolved in 10 cc. of pyridine and heated on a steam bath for 1 hour. The solution was then allowed to cool and was poured into a mixture of water and ice containing 11 cc. of concentrated hydrochloric acid. An oil that precipitated out was taken up in ether; the ethereal solution was washed with dilute sulphuric acid, a dilute solution of sodium bicarbonate, and then with water; and the solution was dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the residue (4.26 g.) was chromatographed through silica gel; three products were obtained. Benzene and ethyl ether (19:1) eluted 1.3 g. of triphenyl carbinol (m.p. and mixed m.p. 162°). Ethyl ether eluted

0.98 g. of the monotrityl ether of (VII) while 1.97 g. of VII ($R = n\text{-C}_{10}\text{H}_{21}$) was recovered from the last fraction. The monotrityl ether, $\text{C}_{10}\text{H}_{21}\text{O}(\text{CH}_2\text{CH}_2\text{O})_6\text{C}(\text{C}_6\text{H}_5)_3$ was a yellowish liquid (b.p. 195° at 0.001 mm. Hg, η_D^{20} 1.5207). Calculated for $\text{C}_{41}\text{H}_{60}\text{O}_7$: C, 74.09%, H, 9.10%; found: C, 74.13%, H, 9.31%.

Reaction between Hexaoxyethyleneglycol Monopotassium Salt and 1-Chlorododecane

The reaction was carried out as in the previous case using 28.2 g. (0.1 M.) of the glycol, 3.91 g. (0.1 g-atom) of potassium and 25 g. (0.12 M.) of 1-chlorododecane, η_D^{20} (found) 1.4432, η_D^{20} (reported in literature) 1.44255 (14). The mixture became neutral after 2 hours, acetone was added, and the potassium chloride was removed by filtration. The acetone was evaporated off, and the remaining solution was distilled under reduced pressure. After the excess of reagent had distilled over, there was obtained hexaoxyethyleneglycol monododecyl ether (VII, $R = n\text{-C}_{12}\text{H}_{25}$, 22.4 g., 50%; b.p. 216° at 0.002 mm. Hg). The residue was chromatographed through silica gel and ethyl ether eluted 6.7 g. (10.8%) of crystalline didodecyl ether (VIII, $R = n\text{-C}_{12}\text{H}_{25}$), which was recrystallized from absolute ethyl alcohol; m.p. 33.5° .

The trityl ether from the monododecyl ether was prepared as described before, separated by chromatography, and further purified by distillation; (b.p. 155° at 0.001 mm. Hg, η_D^{20} 1.5188). Calculated for $\text{C}_{43}\text{H}_{64}\text{O}_7$: C, 74.53%, H, 9.31%; found: C, 74.82%, H, 9.36%.

*Preparation of Hexaoxyethyleneglycol *n*-Tetradecyl Ethers*

The reaction was carried out as above using 22.56 g. (0.08 M.) of the glycol, 3.13 g. (0.08 g-atom) of potassium, and 25 g. (0.09 M.) of 1-bromotetradecane, η_D^{20} (found) 1.4602, η_D^{20} (reported in literature) 1.4608 (8). After the mixture had become neutral, it was submitted to fractional distillation under 0.02 mm. Hg. The first two fractions were the unreacted reagents, *n*-bromotetradecane (b.p. 75° at 0.02 mm. Hg) and hexaoxyethyleneglycol (b.p. 156° at 0.02 mm. Hg), and the third fraction was hexaoxyethyleneglycol monotetradecyl ether (VII, $R = n\text{-C}_{14}\text{H}_{29}$, b.p. 195° at 0.02 mm. Hg, 14.3 g., 33.1%), which crystallized on cooling and was recrystallized from acetone; m.p. 35° . The residue from the distillation was fractionated by chromatography through a column of silica gel and there were obtained, from elution with ethyl ether, crystals of the ditetradecyl derivative (VIII, $R = n\text{-C}_{14}\text{H}_{29}$; 8.9 g., 29.2%), which were recrystallized from absolute ethyl alcohol; m.p. 43° .

The trityl derivative from the monoether was prepared as above, separated through a column, and distilled (b.p. 195° at 0.001 mm. Hg). Calculated for $\text{C}_{35}\text{H}_{68}\text{O}_7$: C, 74.9%, H, 9.51%; found: C, 74.0%, H, 9.25%.

*Preparation of *p*-(1,1,3,3-Tetramethylbutyl)phenyl- β -chloroethyl Ether (XII)*

A mixture of *p*-(1,1,3,3-tetramethylbutyl)phenol (IX) (74 g., 0.36 M.), sodium hydroxide (14 g., 0.36 M.), and 30 cc. of water was stirred vigorously and heated at 100° in a water bath for 10 minutes. Dioxane (30 cc.) was then added to dissolve the sodium phenate completely, and β -chloroethyl toluene-*p*-sulphonate (X) (85 g., 0.36 M.) was added slowly over a 2 hour period. After another hour's heating and stirring, enough sodium hydroxide (10%) was added to neutralize completely the *p*-toluene sulphonic acid (XI) formed. The mixture was then distilled with steam. The residue from the steam distillation was extracted with benzene and dried over potassium carbonate. The solvent was evaporated and the residue (96 g.) was distilled under reduced pressure.

There was obtained 90 g. (93%) of *p*-(1,1,3,3-tetramethylbutyl)phenyl- β -chloroethyl ether (XII) as a colorless liquid (b.p. 98° at 0.005 mm. Hg, η_D^{23} 1.5124). Calculated for: $C_{16}H_{25}OCl$: C, 71.50%, H, 9.31%, Cl, 13.2%; found: C, 71.62%, H, 9.32%, Cl, 12.7%.

Its infrared spectrum showed the typical aromatic bands at 6.2 μ (C=C stretching) and the strong band in the 12 μ region indicative of a *p*-substituted phenyl ring, a band at 8 μ corresponding to an aromatic ether, and the typical absorptions of the *t*-butyl groups at 7.35 μ .

Preparation of Heptaoxyethyleneglycol Mono-p-(1,1,3,3-tetramethylbutyl)phenyl Ether (XIII)

The monopotassium salt of hexaoxyethyleneglycol was prepared as described previously using 56.4 g. (0.2 M.) of glycol and 7.8 g. (0.2 g-atom) of potassium. This was condensed with 58.7 g. (0.21 M.) of the chloroether (XII). The potassium chloride was removed by filtration and the excess reagents were distilled under reduced pressure. The residue (20.92 g.) was chromatographed in two portions through silica gel. There was obtained 16.41 g. (16%) of heptaoxyethyleneglycol mono-*p*-(1,1,3,3-tetramethylbutyl)phenyl ether (XIII) as a colorless liquid and 5.74 g. of (XIV) as a semisolid of waxy appearance; calculated for $C_{32}H_{50}O_7$: C, 80.7%, H, 10.5%; found: C, 80.9%, H, 10.5%. The monoether could not be crystallized but was distilled (b.p. 125° at 0.001 mm. Hg).

A monotrityl derivative of (XIII) was prepared in the usual manner. The product was separated by chromatography and distilled twice to give a yellowish liquid (b.p. 230° at 0.001 mm. Hg, η_D^{20} 1.5447). Calculated for $C_{47}H_{64}O_8$: C, 74.60%, H, 8.46%; found: C, 74.46%, H, 8.36%.

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MERCURY PHOTOSENSITIZED DECOMPOSITION OF BUTYLENE OXIDE¹

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ABSTRACT

Mercury photosensitized decomposition of *trans*-2,3-epoxybutane has been studied at 25°. The quenching efficiency of this compound is 1.23 relative to the quenching efficiency of N₂O taken as unity; the quenching cross section is, therefore, 19 Å² (taking 3.6 Å² for the quenching cross section of *n*-butane). The main products formed are isobutanol, C₂H₆, CO, C₂H₄, C₃H₈, CH₃CHO, C₂H₅CHO, CH₃COC₂H₅, CH₄, and H₂. The yields of most of the products decrease with increasing pressure while those of C₂H₆, CH₄, and H₂ remain essentially pressure independent. Possible reaction mechanisms are discussed.

INTRODUCTION

Mercury photosensitized decomposition of different organic and inorganic compounds frequently provides a convenient source of free radicals and atoms and may be of considerable value for the study of elementary chemical reactions. The usefulness of this technique is largely dependent on the knowledge of the primary steps in the process. While important progress has been made in an attempt to draw general conclusions from the available experimental results (14), further advance might be expected from more extensive comparisons between and within different series of compounds, particularly of organic compounds containing different functional groups. More experimental information of this nature, is, therefore, desirable.

In a previous publication the results of a study of the mercury photosensitized decomposition of ethylene oxide were reported (3). The quenching efficiency of this compound was found to be much smaller than of some other oxygen containing compounds as, for example, of acetaldehyde, which is isomeric with it. The major primary process, the splitting of the molecule into CH₃ and HCO radicals, necessarily involved the opening of the epoxide ring and migration of an H-atom prior to the decomposition. The existence of at least one more primary process was established and also a close similarity of the over-all course of the reaction with the reaction of oxygen atoms with ethylene.

The present work was undertaken in an attempt to obtain further information on quenching by epoxides and to establish whether there is in general a similarity between the mercury photosensitized reaction of epoxides and the reaction of oxygen atoms with the corresponding olefins. An epoxybutane was chosen for this purpose since the mechanism of interaction and the products formed when oxygen atoms add to butene are now known (5).

EXPERIMENTAL

The experimental arrangement employed has been described before (3). For the analysis of products use was made of a Le Roy still (12), gas-liquid partition chromatography (GLPC) (2), and infrared and mass spectroscopy.

A sample of *trans*-2,3-epoxybutane was kindly supplied by the Distillers Company, Ltd., Great Burgh, Epsom, Surrey, Great Britain. It was used after repeated bulb to bulb distillation *in vacuo*. No appreciable amounts of impurities were detected by GLPC analysis. Oxygen was produced by heating research grade KMnO₄.

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The intensity of the low pressure mercury arc used was determined on the basis of H_2 production from 200 mm. of *n*-butane, for which Bywater and Steacie (1) have found a quantum yield of 0.50 at 25° C.

RESULTS

(a) Quenching Efficiency

The method described previously (4) was used to determine the relative over-all quenching efficiency of *trans*-2,3-epoxybutane. The plots of reciprocal quantum yields

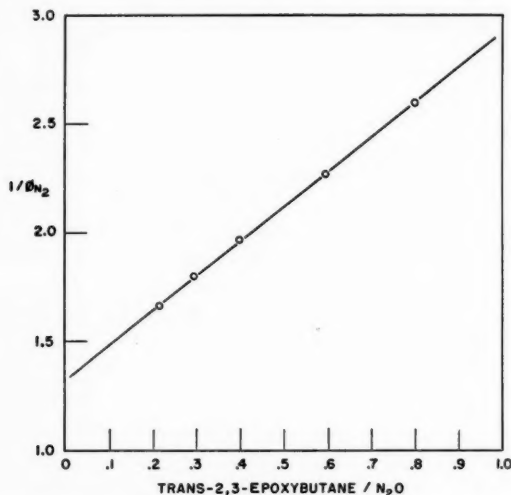


FIG. 1. Plot of the reciprocal quantum yield of nitrogen production against the ratio of the concentrations of *trans*-2,3-epoxybutane and nitrous oxide (100 mm. N_2O , $24 \pm 1^\circ C.$, irradiation time 120 minutes, mean I_a 3.54×10^{15} quanta/second).

of nitrogen production for various ratios of *trans*-2,3-epoxybutane and nitrous oxide are given in Fig. 1. The pressure of nitrous oxide in these experiments was 100 mm., the temperature $24 \pm 1^\circ C.$, the exposure 120 minutes, and the mean light intensity 3.54×10^{15} quanta/second. The slope to intercept ratio of the plot gives 1.23 as the value of the ratio of the over-all quenching efficiency of the epoxide to that of nitrous oxide. With the previous choice of 3.6 \AA^2 for the quenching cross section of *n*-butane (4) this leads to 18.9 \AA^2 as the quenching cross section of *trans*-2,3-epoxybutane.

(b) Photosensitized Decomposition of *trans*-2,3-Epoxybutane

The main products observed in the mercury photosensitized decomposition of *trans*-2,3-epoxybutane were carbonyl compounds, C_2H_6 , CO, C_2H_4 , C_3H_8 , H_2 , and CH_4 . Smaller amounts of *n*-butane and isobutane were found also, at least at larger conversions, as well as traces of some other compounds. The quantum yields of the various products as a function of the extent of conversion at an initial pressure of 20 mm. are shown in Fig. 2. Notable is the pronounced decline with reaction time in the yields of C_2H_4 and of the carbonyl compounds. The latter compounds have been determined from infrared absorption measurements at a single wave length and on the basis of calibration

with a single carbonyl compound. Since, however, they are mixtures of several compounds there may be some doubt with regard to the absolute values of their quantum yields given in Fig. 2. At an initial pressure of 10 mm. *trans*-2,3-epoxybutane it was possible to analyze for these compounds by GLPC. The results are shown in Fig. 3 together with some values for CO, C₂H₆, C₃H₈, and C₂H₄. At low conversions the main

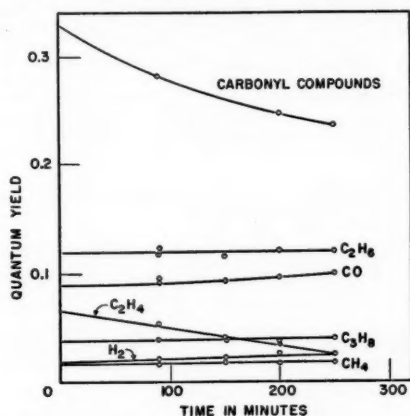


FIG. 2. Effect of the extent of reaction on the products of the mercury photosensitized decomposition of *trans*-2,3-epoxybutane at an initial pressure of 20 mm.

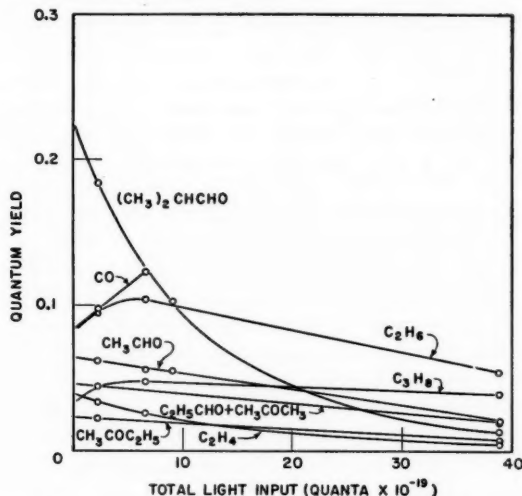


FIG. 3. Effect of the extent of reaction on the products of the mercury photosensitized decomposition of *trans*-2,3-epoxybutane at an initial pressure of 10 mm.

product is isobutanol. Appreciable amounts of acetaldehyde, propanal, and methyl ethyl ketone are also formed, and perhaps at larger conversions also some acetone (not identified with certainty). There is a rapid decline in the yield of isobutanol with the reaction time and similarly in the yield of ethylene. These experiments have been extended to very high conversions using exposures of up to 16 hours with simultaneous illumination

at both ends of the reaction cell. With such long reaction times small amounts of *cis*-2,3-epoxybutane are also found, as will be discussed later.

The effect of pressure of *trans*-2,3-epoxybutane is shown in Fig. 4 (open circles). The values at 20 and 10 mm. are the extrapolations to zero conversions from Figs. 2 and 3, respectively. Such extrapolations are necessarily somewhat uncertain. The remaining values have been determined at relatively low conversions. After the usually observed initial increase in quantum yields, at still higher pressures the yields of some of the products (C_2H_6 , CH_4 , H_2) appear to remain approximately constant while those of the

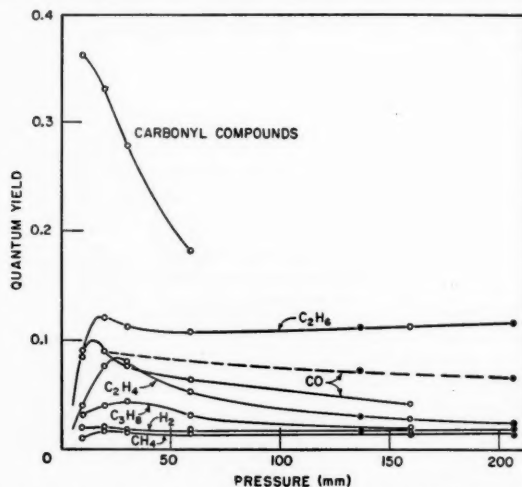


FIG. 4. Effect of pressure of *trans*-2,3-epoxybutane (open circles) and of carbon dioxide added to 20 mm. of *trans*-2,3-epoxybutane (filled circles) on the products of the mercury photosensitized decomposition of *trans*-2,3-epoxybutane.

other products decrease. With large amounts of CO_2 added to 20 mm. of *trans*-2,3-epoxybutane (filled circles) the quantum yields had to be calculated after allowing for quenching by CO_2 . This was done on the basis of the literature value (16) for the quenching cross section of CO_2 and the present value for *trans*-2,3-epoxybutane. It should be stressed that the two values have been determined by two widely different methods and the good coincidence of most of the yields corrected for quenching by CO_2 with those obtained with the corresponding pressures of *trans*-2,3-epoxybutane alone may be to some extent fortuitous. With CO_2 added, the quantum yields of CO, evaluated in this manner, are somewhat higher than those obtained with the epoxybutane alone. It is significant, however, that again the yields of CO and C_2H_4 decline with increasing pressure while those of C_2H_6 , CH_4 , and H_2 remain approximately constant. With large amounts of CO_2 added, no attempt was made to analyze for C_3H_8 and the carbonyl compounds.

The effect of large amounts of argon added to 10 mm. of *trans*-2,3-epoxybutane on the yields of the carbonyl compounds, determined by GLPC analyses, is shown in Table I. In the presence of argon the quantum yields of carbonyl compounds show a general decrease, more conspicuous at lower conversions, where it is presumably less masked by secondary effects. On the other hand, the yield of *cis*-2,3-epoxybutane is distinctly increased.

TABLE I

EFFECT OF ADDITIONS OF ARGON AND OF OXYGEN ON THE QUANTUM YIELDS OF SOME OF THE PRODUCTS (10 mm. *trans*-2,3-epoxybutane, $25 \pm 1^\circ \text{C}$.)

Added gas	Light input (quanta $\times 10^{-19}$)	Quantum yields								
		CH ₄	CO	C ₂ H ₆	C ₂ H ₄	CH ₃ -CHO	C ₂ H ₅ CHO +CH ₃ COCH ₃	iso-C ₃ H ₇ CHO	CH ₃ -COC ₂ H ₅	<i>cis</i> -2,3-C ₄ H ₈ O
A, 408 mm.	8.0	N.d.*	N.d.	N.d.	N.d.	0.037 (0.056)†	0.023 (0.041)	0.057 (0.112)	0.014 (0.020)	0.005 ₃ —
A, 592 mm.	41.2	N.d.	N.d.	N.d.	N.d.	0.018 (0.021)	0.015 (0.020)	0.012 (0.014)	0.006 ₂ (0.007 ₂)	0.004 ₅ (0.0019)
O ₂ , 0.5 mm.	5.9	0.011 (0.023)	0.405 (0.119)	0.010 (0.104)	0.002 (0.027)	0.053 (0.058)	0.000 (0.027)	0.021 (0.133)	N.d. (0.021)	— —

*N.d. = not determined.

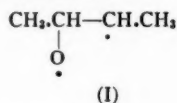
†The values in parentheses are the corresponding yields in the absence of added gases, based on Fig. 3.

One experiment was carried out in which O₂ was added in the course of the sensitized decomposition of 10 mm. *trans*-2,3-epoxybutane in frequent small doses so that the pressure of O₂ was maintained at about 0.5 mm. The concentration of oxygen had to be kept relatively low in order to avoid appreciable direct quenching by this compound. Some of the results are shown in Table I. A large increase in CO yield was observed and there was a drastic decrease in the yields of the other products. Large amounts of oxygen were consumed ($\phi \approx 1.4$) and methanol, not observed in the absence of O₂, was found to be a major product ($\phi \approx 0.4$). The results thus indicated the important role in this process of free radicals and in particular of methyl radicals. The yield of acetaldehyde remained essentially unaltered in the presence of oxygen although this could not be taken as a positive proof of a direct molecular formation of this compound since it may also be a secondary product in the presence of oxygen. Similarly, the incomplete suppression of CH₄, C₂H₆, etc., should not be taken as a proof of a dual manner of formation of these compounds. With the intermittent replenishment of the oxygen consumed in the process it is possible that during part of the reaction time the concentration of oxygen might have been quite low.

Formation of CH₃ radicals as a major primary product is strongly indicated by the above results. This has been further confirmed by direct detection of these radicals in large amounts in the mass spectrometer in an experiment kindly performed by Dr. F. P. Lossing with the use of an experimental technique recently developed (9).

DISCUSSION

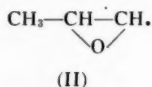
In the reaction of oxygen atoms with either *trans*- or *cis*-butene-2 very little decomposition of the initially formed biradical (I)



takes place and the reaction products consist essentially entirely of the following four compounds (5, 6): *cis*- and *trans*-2,3-epoxybutane, isobutanal, and methyl ethyl ketone. These products are formed by molecular rearrangement of the biradical (I) and not by combination of free radicals. In contrast to the relatively simple course of these reactions, the mercury photosensitized decomposition of *trans*-2,3-epoxybutane is quite complex.

This complexity precludes a quantitative treatment of the experimental results obtained and only a qualitative discussion is possible at present.

The yields of some of the products of the photosensitized decomposition of *trans*-2,3-epoxybutane are strongly suppressed as the pressure is increased while those of the other products, notably of ethane, are affected very little. Methyl radicals undoubtedly play an important role in the process. In view of this it is worth while first to enquire whether an assumption of a predominant but not necessarily exclusive initial formation of methyl radicals, not suppressed by increasing pressure, is sufficient to explain the experimental observations. The decrease of the yields of some of the products at higher pressures would then have to be explained by assuming that the remainder of the molecule, the fragment C_3H_5O , can lose its excess energy on collisions and be stabilized into the radical (II),



while at lower pressures it can readily isomerize into the radical $CH_3\dot{C}H.CHO$ (and possibly, to a much smaller extent, into $CH_3.CO.CH_2$) or decompose into C_2H_4 and CHO . The last of these radicals is known to decompose readily into CO and H ; it can also combine with CH_3 and C_2H_5 to give CH_3CHO and C_2H_5CHO , respectively (3). The major product of the process, isobutanol, could be formed by combination of CH_3 and $CH_3\dot{C}H.CHO$ and its formation, as well as that of CO , C_2H_4 , C_3H_8 , and of the other carbonyl compounds should, therefore, decrease with increasing pressure, as observed. Propane could result from CH_3 and C_2H_5 and the latter from H and C_2H_4 . Methane and hydrogen are produced in relatively small amounts and the approximate pressure independence of their yields is perhaps due to the fact that H -abstraction from β -butene oxide appears to be quite slow at 25° so that the necessary hydrogen is probably obtained mainly from HCO radicals. It is also possible that CH_4 and H_2 result at least partly from a direct intramolecular rearrangement, as was shown to be the case with H_2 in the photosensitized decomposition of ethylene oxide (3).

The predominantly free radical mechanism just discussed can, therefore, explain qualitatively the main experimental observations. It is also necessary, however, to assume that at higher pressures the stabilized radicals (II) combine largely with CH_3 radicals to regenerate the *trans*-2,3-epoxybutane while the *cis* isomer is formed only in minor amounts. This assumption should be verified by the use of *cis*-2,3-epoxybutane as the initial reactant. In the present work a pronounced *increase* in the yield of the *cis* isomer has been observed on addition of large amounts of argon, although even then the yield was relatively small. The products formed by combination of C_3H_5O radicals between themselves, as would be required by this mechanism, would be of too low volatility to be observed by the methods employed in this work.

It is of interest that Gomer and Noyes (10) and Trotman-Dickenson and Steacie (15) have observed previously a complex behavior of the $CH_2-\dot{C}H$ radical, obtained



through hydrogen abstraction from ethylene oxide, which may be regarded as the first member of the series of which the radical (II) represents the next higher member.

An alternative mechanism can be formulated by assuming two distinct and approximately equally important primary steps: (1) formation of a very short lived excited

molecule which always decomposes into radicals or stable molecules, and (2) formation of a second excited molecule which is sufficiently long lived to be capable of collisional deactivation at higher pressures. In view of the pronounced effect of oxygen, the long lived excited molecules would then have to be assumed to be able also to react rapidly with oxygen molecules to give products different from those normally formed.

A comparison of the quenching efficiencies of the two epoxides studied so far with those of the corresponding olefins and paraffins is given in Table II. The quenching

TABLE II
COMPARISON OF THE OVER-ALL QUENCHING EFFICIENCIES (q) OF OLEFINS,
EPOXIDES, AND PARAFFINS
(Relative to the quenching efficiency of C_2H_4 taken as unity)

Compound	q	Compound	q
$H_2C=CH_2$	1	$CH_3CH=CH.CH_3$	1.1*
H_2C-CH_2 \diagup \diagdown O	0.10	$CH_3CH-CH.CH_3$ \diagup \diagdown O	0.59
$H_3C.CH_3$	0.004	$CH_3.CH_2.CH_2.CH_3$	0.12

* Calculated from the data of Darwent, Phibbs, and Hurtubise (Ref. 8).

efficiency of ethylene is taken as unity. The quenching efficiencies of the epoxides lie between those of the paraffins and the olefins and are somewhat closer to the latter. They show a large increase as the molecule becomes larger, and are similar in that respect to the paraffins (7, 8). The primary chemical process, however, is not the rupture of a C—H bond, as in paraffins, but resembles in some ways the processes observed with some olefins and carbonyl compounds.

It is believed that in the interaction of $Hg\ 6(^3P_1)$ atoms with olefins triplet olefin molecules are formed while in the case of paraffins there are no sufficiently low-lying triplet levels for this to occur (11). The energy of 112 kcal./mole available from the $Hg\ 6(^3P_1)$ atoms ought to be well in excess of the energy necessary for the opening of the epoxide ring in *trans*-2,3-epoxybutane. The formation of the triplet biradicals (I), a quenching process which would satisfy the spin conservation rule (11), could then be anticipated. The difference between the behavior of these biradicals and those formed when oxygen atoms add to butene-2 may be explained by the difference in the vibrational excitation in the two cases. If the heat of reaction of oxygen atoms with *trans*-butene-2, to give the biradical (I) is A kcal./mole, then this energy represents approximately the excess vibrational energy possessed by the biradical when formed. This energy is evidently insufficient to decompose the biradical to any extent before it degrades to the four compounds formed as the final product of the reaction. If the same biradical is formed initially from *trans*-2,3-epoxybutane on transfer of 112 kcal. from $Hg\ 6(^3P_1)$ atoms, the excess energy is likely to be $A + 20$ to 30 kcal., i.e., some 20 to 30 kcal. greater.* This excess of vibrational energy might be sufficient to lead to a rapid decomposition of the biradical into a CH_3 and a C_3H_5O fragment or, alternatively, to an internal rearrangement. An analogous explanation can reconcile the various primary processes established recently for some simple olefins by Lossing, Marsden, and Farmer

* The heats of reaction of oxygen atoms with C_2H_4 , C_3H_6 , and *trans*- C_4H_8 -2 to give ethylene oxide, CH_3CHO , C_2H_5CHO , CH_3COCH_3 , and $CH_3COC_2H_5$ are 87, 114, 113, 116, and 114 kcal./mole, respectively.

(13) with an initial interaction of the Hg $6(^3P_1)$ atoms with the CC double bonds in those compounds.

In conclusion it should be emphasized that while the study of the mercury photo-sensitized decomposition of ethylene oxide and *trans*-2,3-epoxybutane has revealed some interesting trends, other members of the epoxide series ought to be investigated before generalizations can be made with certainty.

ACKNOWLEDGMENT

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REACTIONS OF SULPHONIC ESTERS

VI. THE TEMPERATURE DEPENDENCE OF THE RATE FOR THE HYDROLYSIS OF A SERIES OF ALKYL BENZENESULPHONATES¹

R. E. ROBERTSON

ABSTRACT

Data are presented showing temperature dependence of the rate of hydrolysis of methyl, ethyl, isopropyl, and *n*-propyl benzenesulphonates in water. The heat of activation is shown to be temperature dependent to the extent of -30 to -40 cal./mole deg. Since, in solvolysis, the properties of water favor ionization over nucleophilic displacement, it is suggested that these temperature coefficients, ΔC_p^\ddagger , and the accompanying entropy differences, ΔS^\ddagger , can be rationalized in terms of variations in the reorganization of the solvent about the transition state.

This paper is the first of a series in which we shall examine the changes in the thermodynamic parameters characterizing solvolysis which result from simple structural changes in the ester. Here, we examine the effect of α -methylation in the series methyl, ethyl, and isopropyl benzenesulphonate; stepwise structural changes which should cause each successive ester to react by a mechanism approaching more closely the limiting S_N1 type. Data for the *n*-propyl ester are included for comparison with the α -methylated series and to extend our earlier investigation of straight chain effects in this series (23).

The formation of a quasi-ionic transition state from the unchanged ester will certainly result in a reorganization of solvent molecules, the extent depending on the particular ester and on the degree of charge separation in the transition state. It is reasonable to expect this reorganization to determine, in part, the changes in the values of the thermodynamic parameters which characterize the activation process, particularly in the entropy (ΔS^\ddagger) and the heat capacity (ΔC_p^\ddagger). Theoretical reasons for expecting a change in the heat capacity in such reactions have been given many years ago (22) and experimental evidence showing that

$$d\Delta H^\ddagger/dT \neq 0$$

for solvation reactions has recently been reviewed by Bensley and Kohnstam (1). In every example known, the sign of ΔC_p^\ddagger for solvolysis of esters is negative and of the same sign and magnitude as found for the analogous ionization of weak acids (7). Since the values of ΔC_p^\ddagger are so large there seems no reason to doubt that the observed heat capacity changes which characterize both processes arise in large part from the reorganization of solvent molecules, and our consideration of the differences in the kinetic parameter, ΔC_p^\ddagger , will be based on this assumption.

EXPERIMENTAL

The experimental procedures and methods of calculation have already been described in detail (29, 19) and need not be repeated here save to note the introduction of an amplifier (GR-1231-B) into the separate Wagner earthing circuit. This deserved mention, since it permitted a more precise balancing and proved particularly advantageous where several runs were being followed simultaneously.

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Methyl benzenesulphonate, Eastman White Label, was repeatedly fractionated by fractional freezing to give a product with a constant melting point -4.50°C . Ethyl, *n*-propyl, and isopropyl benzenesulphonates were synthesized by the method of Morgan and Cretcher (26) from purified starting materials and redistilled under vacuum to give products with properties identical with those already published (28).

The initial concentration of the methyl and ethyl esters in kinetic rate studies was about 0.2 g./liter but this was reduced to 0.1 g./liter for the propyl esters because of the lower solubility of the latter. A single stock solution of distilled water containing 0.2 g./liter of benzenesulphonic acid as a supporting electrolyte was used throughout the study. Efforts were made to study the rates over the same average low ionic concentration and similar concentration changes in order to minimize salt effects.

RESULTS

Average rate data from *n* concurrent runs at each temperature are collected for the four esters in Tables I, II, III, and IV. The average deviation of the rates is given in

TABLE I
KINETIC DATA FOR THE HYDROLYSIS OF METHYL BENZENESULPHONATE IN WATER

Temp., $^{\circ}\text{C}$.	$k_{1(\text{obs.})}\text{sec.}^{-1}\times 10^5$	Av. dev.	<i>n</i>	$k_{1(\text{calc.})}\times 10^5$	$k_{1(\text{obs.})} - k_{1(\text{calc.})}$
9.752	0.153 ₃	± 0.0003	4	0.1538	-0.0005
14.991	0.317 ₈	0.0009	3	0.3175	+0.0003
19.988	0.617 ₄	0.002	3	0.6158	+0.0016
24.981	1.16 ₅	0.001	4	1.162	+0.003
29.402	1.99 ₈	0.004	3	1.998	0.00
40.036	6.80	0.03	4	6.88	-0.008
50.003	19.6 ₅	0.06	3	19.65	-0.00
55.075	32.6 ₁	0.08	4	32.69	-0.08
60.026	52.6 ₈	0.10	3	52.75	-0.09
64.998	83.8 ₈	0.20	3	83.78	+0.10
69.996	131.4	0.4	3	131.1	+0.3

TABLE II
KINETIC DATA FOR THE HYDROLYSIS OF ETHYL BENZENESULPHONATE IN WATER

Temp., $^{\circ}\text{C}$.	$k_{1(\text{obs.})}\times 10^5$	Av. dev.	<i>n</i>	$k_{1(\text{calc.})}\times 10^5$	$k_{1(\text{obs.})} - k_{1(\text{calc.})}$
9.754	0.126 ₈	± 0.0006	3	0.1270	-0.0004
14.991	0.268 ₀	0.0001	3	0.2674	-0.0006
19.988	0.52 ₈	0.0016	3	0.5281	+0.0000
24.981	1.01 ₉	0.0015	3	1.014	+0.005
30.020	1.90 ₈	0.01	3	1.908	+0.000
39.855	6.0 ₈	0.04	3	6.104	-0.024
49.990	18.4 ₈	0.016	5	18.48	-0.00
55.075	31.2 ₃	0.03	3	31.21	0.02
60.026	50.9 ₈	0.1	3	51.00	-0.04
64.781	80.4	0.2	2	80.36	-0.04
69.996	130.4	0.4	3	120.0	+0.2
74.870	200.2	0.8	3	200.3	-0.1

column 3 of each table. Values of the constants for equation [1] were

$$[1] \quad \log_{10} k = A/T + B \log_{10} T + C,$$

calculated from these data directly by the method of least squares. These values are collected in Table V.

TABLE III
 KINETIC DATA FOR THE HYDROLYSIS OF ISOPROPYL BENZENESULPHONATE IN WATER

Temp., ° C.	$k_{1(\text{obs.})}\text{sec.}^{-1}\times 10^5$	Av. dev.	<i>n</i>	$k_{1(\text{calc.})}\text{sec.}^{-1}\times 10^5$	$k_{1(\text{obs.})}-k_{1(\text{calc.})}$
0.000	1.917	±0.005	3	1.914	+0.003
2.500	2.822	0.006	3	2.827	-0.005
5.005	4.140	0.001	3	4.142	-0.002
7.467	6.016	0.012	3	5.981	+0.035
9.940	8.544	0.010	4	8.594	-0.050
14.993	17.50	0.035	4	17.53	-0.03
19.985	34.41	0.09	3	34.46	-0.05
19.992	34.58	0.03	4	34.47	-0.11
22.485	47.86	0.08	3	47.78	+0.08
24.899	64.95	0.9	5	65.12	-0.17
24.908	65.14	0.04	4	65.195	-0.055
27.486	90.19	0.13	3	90.125	+0.065
30.105	124.4	0.007	3	124.34	+0.06
32.493	166.5	1.0	3	165.7	+0.8
35.002	222.2	0.5	4	222.8	-0.6

 TABLE IV
 KINETIC DATA FOR HYDROLYSIS OF NORMAL PROPYL BENZENESULPHONATE IN WATER

Temp., ° K.	$k_{1(\text{obs.})}\text{sec.}^{-1}\times 10^5$	<i>n</i>	$k_{1(\text{calc.})}\text{sec.}^{-1}\times 10^5$	$k_{1(\text{obs.})}-k_{1(\text{calc.})}$
19.993	0.414 ₀ ± 0.0013	3	0.4143	-0.003
29.932	1.43 ₁ ± 0.004	3	1.436	-0.001
39.840	4.52 ₆ ± 0.008	3	4.514	+0.012
50.054	13.3 ₉ ± 0.14	3	13.39	0.00
60.034	36.1 ₅ ± 0.14	3	35.96	-0.19
75.006	140.0 ± 0.5	3	140.0	0.000
80.006	213.0 ± 0.1	3	213.1	-0.1

 TABLE V
 SUMMARY OF CONSTANTS FOR EQUATION [1]

Benzenesulphonate	<i>A</i>	<i>B</i>	<i>C</i>
Methyl	-6860.442	-15.81888	57.2186
Ethyl	-7063.212	-16.37588	59.2178
Isopropyl	-7454.790	-19.74238	70.6734
<i>n</i> -Propyl	-6734.056	-14.73970	53.9527

Rates corresponding to the experimental temperatures were calculated from these derived constants according to equation [1] and are included along with the differences ($k_{\text{obs.}} - k_{\text{calc.}}$) in the respective tables. A comparison of the average deviations with the corresponding deviation from the calculated rate shows both deviations are of the same magnitude at a given temperature, thus justifying the use of equation [1] which assumes that

$$d\Delta C_p^\ddagger/dT = 0.$$

Somewhat better agreement would probably be achieved by further refinement of our experimental method but such steps are not warranted at this time.

In order to compare our results with those of Tommila and Lindholm (34, 35) we computed the rates at 25° and 50° C. for the four esters (Table VI). Tommila and Lindholm derive Arrhenius parameters from their data in the range 25° to 60° C. to get values

TABLE VI
 SUMMARY OF DERIVED THERMODYNAMIC QUANTITIES AT 298.16° K.

Benzenesulphonic ester	Methyl	Ethyl	Isopropyl	n-Propyl
$k_1 \text{ sec.}^{-1} \times 10^5$	1.166*	1.016†	26.27	0.785
$\Delta F^\ddagger \text{ cal.}$	5,912	6,730	4,885	6,696
$\Delta H_0^\ddagger \text{ cal.}$	31,391	32,319	34,098	30,813
$\Delta H^\ddagger_{298.16} \text{ cal.}$	21,420	22,080	21,810	21,490
$-\Delta C_p^\ddagger \text{ cal./mole deg.}$	33.4	34.5	41.2	31.3
Standard error in $\Delta C_p^\ddagger \pm$	1.1	1.4	0.5	0.7
$-\Delta S^\ddagger \text{ cal./mole deg.}$	9.29	7.51	1.81	9.87

* Compared to 1.15 and † 1.03 Tommila and Lindholm (34).

of $E = 21,030 \text{ cal.}$ and $\log PZ = 10.48$ for the hydrolysis of methyl benzenesulphonate. Corresponding values calculated by the method of least mean squares from data in Table I lead to values of $E = 21,600$ and $\log PZ = 10.8928$ over the range $10^\circ\text{--}70^\circ \text{C.}$ The value for $\Delta H^\ddagger_{313.66} + RT$ is 21,467 cal. In spite of such agreement the application of the Arrhenius equation must be regarded as but a roughly approximate expression of the temperature dependence of the rate (30) since there it is assumed, contrary to experimental facts, that $d\Delta E/dT = 0$.

The thermodynamic quantities for the hydrolysis of the four esters were computed from the corresponding constants (Table V) where

$$A = -(\Delta H_0^\ddagger/2.303 R),$$

$$B = (\Delta C_p^\ddagger/R + 1),$$

$$C = (\Delta S_0^\ddagger - \Delta C_p^\ddagger/2.303 R + \log_{10} k/h).$$

Common usage coupled with the practical advantage in connection with the calculation of the entropy led to the adoption of the Eyring transition state nomenclature.*

DISCUSSION

The process of solvolysis for esters of strong acids has frequently been discussed in terms of an intermediate mechanism in which nucleophilic displacement and the factors favoring ionization are complementary (2, 18, 20, 36, 33). While there appears to be no common agreement as to the range of mechanism to be regarded as intermediate it should be obvious that this classification supplements rather than replaces the S_N1 – S_N2 classification of Hughes and Ingold (21). By definition a mechanism is of the limiting S_N1 type where no nucleophilic displacement can be detected in the rate determining step; hence the intermediate mechanism may be regarded as a more detailed description of the older S_N2 classification applicable to those reactions where the tendency toward ionization is significant. It thus serves the useful purpose of emphasizing the contribution of the whole solvent shell to the process of activation rather than concentrating attention on the varying contribution of a single nucleophilic species. This change of emphasis is desirable when discussing the mechanism of solvolysis where the nucleophiles are weak and particularly so in this study of the hydrolysis of benzenesulphonic esters in water.

The low nucleophilicity of water together with its excellent ionizing properties provide

*In this connection we wish to acknowledge discussions with Professor H. C. Brown, Professor J. Halpern, Professor K. J. Laidler, Professor A. Streitwieser, Jr., and Dr. K. O. Kutschke. The values obtained by this method compared with that employed previously (29) are identical for ΔH_0^\ddagger , differ by 2 cal./mole deg. in ΔC_p^\ddagger , while ΔS_0^\ddagger does not include $\log_{10} k/h$.

the conditions for solvolysis shifted toward the S_N1 type in character. While the usual kinetic tests for nucleophilic participation are not available in the case of solvolysis, the conclusion that those solvent-solute interactions favoring ionization are important in the solvolysis of the benzenesulphonates is supported by the contrast between the relative rates of solvolysis for these esters in ethanol with those in water and acetic acid (Table IX). The small range of rate change through the series in the latter solvents, the increase at isopropyl, and the relatively small difference between methyl and neopentyl all support the above hypothesis. Unfortunately it is not possible at present to measure the relative importance of nucleophilicity and of ionization in such reactions. The correlation equations of Grunwald and Winstein (16, 36) and of Swain, Mosely, and Scott (32) provide approximate answers but are subject to the limitation that they are based on relative rates. A more complete evaluation will require a comparison of not only the rates but of the heat, entropy, and heat capacity of activation and such a correlation will remain incomplete unless due allowance is made for the initial state differences of the esters compared. Since it is implicit that solvation effects will be of importance in solvolysis and particularly so for reactions in water, we shall review the salient features of aqueous solutions which we believe are pertinent to the discussion of results presented here and to be presented in subsequent papers of this series.

Solvation of the Initial State

The large changes in entropy and heat capacity which characterize the formation of aqueous solutions of non-electrolytes are most conveniently explained in terms of some type of "freezing" presumably involving the formation of a type of dynamic water shell about the solute. This structure has been compared to that in a gas hydrate (3, 12) and is frequently referred to as an "iceberg" formed about the solute. Although other hypotheses exist for the nature of aqueous solutions, notably that of Powell and Latimer (27) and of Eucken (5), we have found the iceberg model most useful in this work. This graphic term carries the connotation of greater rigidity than probably exists but evidence that the relative difference between the solvation of the initial and the transition state remains much the same within a given series over a 50–60° range is seen in the relative constancy of the ratio k_{D_2O}/k_{H_2O} for isopropyl and isobutyl benzenesulphonate and for methyl bromide, isopropyl bromide, and benzyl bromide (24, 25). Further evidence is the fact that over a temperature range of 70–80° we have not detected any appreciable temperature change in ΔC_p^\ddagger for data in this paper or in a previous publication (29). This contrasts with the expectation raised by the findings of Feats and Ives (10) from their study of the ionization of cyanoacetic acid. The latter authors consider their finding

$$d\Delta C_p(\text{ionization})/dT \neq 0$$

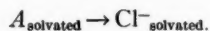
to result from an appreciable change in the water structure in the region 30–40° C. We can only conclude that in so far as such changes exist, the effect is small compared to the changes being observed in hydrolysis.

Molecules which interact strongly with water, such as the alcohols, show greater $-\Delta S_{sol}$ than non-polar molecules, an effect which in this instance may be attributed to hydrogen bonding. Thus qualitative evidence pointing to stronger interaction between the sulphonic ester and water than for the corresponding alkyl halides (25) leads to a picture of the initial state in which the solvation shell is attracted, possibly hydrogen bonded, at two points to the sulphonate group. If the solvation shell did in fact resemble

a unit gas-hydrate (12), such interaction would clearly introduce important modifications in the structure of the shell. For the present problem the most obvious consequence of such attraction will be that in the initial state at least two water molecules will be orientated in a position closer to that which they will occupy in the transition state than in the case of the corresponding alkyl halide, and so will require less reorientation on activation. This conclusion is borne out by the value of k_{D_2O}/k_{H_2O} being closer to unity for the benzenesulphonates and other oxygenated anions than for the alkyl halides (24) and this latter work also provides support for the reasonable hypothesis already stated that, within a given series, solvation differences about the seat of reaction in the initial state are small compared with the changes which arise on activation. It is of interest to note in this connection that Swain and co-workers (32) introduce a constant " c_2 " into their correlation equation to take account of the solvent interaction with the anionic part of the ester and further that (31) there is a close correspondence between these " c_2 " values and the " m " values of the Grunwald, Winstein, and Jones equation, which supposedly represents the whole molecule.

Solvation of the Transition State

Major changes in solvation will obviously arise as the result of the formation of two quasi-ions. In contrast to the large positive heat capacities and relatively large negative entropies which characterize the aqueous solutions of non-electrolytes, monovalent ions of comparable volume have somewhat more positive entropies and large negative heat capacities (4, 11). Since the reactions under consideration involve the change from a non-electrolyte into two quasi-ions, it will be useful to cast a comparison noted by Frank and Evans in the form of an equation and to consider the magnitude of the change in $\Delta S_{(solvation)}$ and $\Delta C_{p(solvation)}$ for the hypothetical reaction of argon converting to chloride ion in water



The entropy and heat capacity changes accompanying the solution process (from the gas phase) are given in Table VII and the differences are the approximate changes in

TABLE VII
THERMODYNAMIC PARAMETERS FOR THE HYPOTHETICAL REACTION

$A \xrightarrow{H_2O} Cl^-$		
	ΔS (cal./mole deg.)	ΔC_p (cal./mole deg.)
Final state ($Cl^-_{solvated}$)	-18.3	-14.5
Initial state ($A_{solvated}$)	-22.6	+43
	ΔS^\ddagger +4.3	ΔC_p^\ddagger -57.5

these parameters due to changes in solvation were the above reaction possible. (We assume the transition state and final state to be similarly solvated.) Using the argument of Frank and Evans (11) the net gain in the entropy on the formation of the ion may be attributed to the "depolymerization" of the water in the area which lies beyond the primary tightly bound layer. The large negative heat capacity change associated with the formation of the ion may be accounted for in part by the decrease in ΔC_p^\ddagger as a consequence of the clamping of a few water molecules by strong electrostatic forces in the

primary solvation layer plus the further loss resulting from the depolymerization phenomenon noted above. While this hypothetical example illustrates the trend to be expected in ΔS^\ddagger and ΔC_p^\ddagger for the creation of a quasi-ionic transition state from a neutral ester, some reasons for expecting quantitative differences in the hydrolysis of a series of benzenesulphonic esters are (a) the ions produced are large compared to Cl^- , (b) though the partial charge may be more diffuse, the total charge may be greater, there being two partial ions, (c) charge separation (development) will vary through the series, (d) water molecules hydrogen bonded in the initial state will reduce effect of reorientation, (e) steric effects will vary through the series and may be expected to have a different relative effect in the initial compared to the transition state.

The number of water molecules forming the solvation shell about the non-electrolyte will obviously be a function of the size of the solute molecule—a fact which may be reflected in the magnitude of both the heat capacity and entropy change characterizing the solution process (11, 13). On activation, charge development will be largely though not entirely localized at the seat of reaction; consequently reorientation will be most evident in this area and will *not* necessarily be proportional to the size of the molecule. This observation is illustrated in the recent paper by Laughton and Robertson (24) comparing the relative rates of solvolysis in light and heavy water. Evidence that the character of the solvation shell remains essentially unchanged in the transition state at a distance of two or three saturated carbon atoms from a charge is seen in the small changes in ΔC_p and ΔS for the ionization process of fatty acids (7). If the creation of a charge led to the collapse of the co-ordinate shell (as might be expected if the solvated molecule resembled a unit gas-hydrate) we would expect large incremental changes in ΔS and ΔC_p as the molecular volume increased; in fact differences become negligible as chain length increases. Further evidence that the solvation shell suffers no large change at a distance of two to three carbon atoms from a created charge is the large positive heat capacity which may be attributed to the alkyl chain of sodium octanoate from a calorimetric determination of the heat of solution by Goddard, Hoeve, and Benson of these laboratories (14). This conclusion is in agreement with that reached by Frank and Evans from a consideration of the entropy change associated with solvation and the fluidities of alkylammonium ions (11, also 17).

Effect of α -Methylation

In this section we shall examine changes in the derived parameters from the hydrolysis of the series $\text{Me} \rightarrow \text{Et} \rightarrow \text{i-Pro}$ benzenesulphonates in terms of the general model discussed in preceding sections.

In reactions of the type discussed here, successive α -methylation leads to an increase in steric hindrance to nucleophilic attack and an increase in electron release to the seat of reaction (21). Both of these effects favor a shift in mechanism toward ionization. The observed rate ratio $\text{Me} = \text{Et} < \text{i-Pro}$ (1:1:24), the equality of the derived ΔH^\ddagger , and the relatively small differences in $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ through the series suggest that either the mechanistic differences here are small, as a consequence of the spectrum of reactions being shifted toward $\text{S}_{\text{N}}1$ type and of the possible smaller steric requirements of water as a nucleophile, or that the small differences result from the cancellation of larger effects. Whatever the cause of the small differences, bond making should certainly be greater in the solvolysis of the primary compared to the secondary esters and hence lead to a stiffer transition state and less charge development (15). Considering the nucleophile

and the ester alone, this should result in a more negative ΔC_p^\ddagger for the methyl ester than for the isopropyl ester, contrary to what is found. Considered as a partial ionization, the differences in solvation arising from differences in size (solvent exclusion) between the methyl and isopropyl quasi-cations would favor a shift in ΔC_p^\ddagger which is likewise the opposite of that observed. But if our model is correct, charge development is not equal and we are led to the hypothesis that the observed negative shift in ΔC_p^\ddagger (Table IX) is the result of an even tighter clamping of water molecules in the solvation shell surrounding the transition state of the isopropyl ester than is suggested by the observed $\Delta\Delta C_p^\ddagger$. Such a hypothesis implies that initial state differences within a given series are of less importance than those arising from differences in charge development, and we have already discussed evidence favoring this assumption. Everett has suggested that the opposition of trends in the ΔS and ΔC_p for the ionization of three methylamines may be attributed to differences of initial state solvation (9) but in this case, it will be noted that the ions (corresponding to the transition state) have equal positive charges. An explanation for the positive trend in the entropy between the secondary and primary esters on hydrolysis based on the relative tightness of the nucleophile-ester bond, alone, appears illogical to us if it is necessary to account for the change in ΔC_p^\ddagger in terms of the clamping down of many water molecules. We have noted above that aqueous solutions of ions are characterized by having more entropy than would be expected; the addition of a charge may even lead to a net increase in entropy (Table VII) though the charge undoubtedly would result in the tighter binding of some of the solvent molecules. Exclusion of solvent from the seat of reaction in the transition state, as suggested by Evans and Hamann (6), is probably a factor but this would also lead to a positive trend in ΔC_p^\ddagger if this were the controlling factor. In any case evidence from the ratio of solvation rates in light and heavy water suggest that solvation of the cationic part of the transition state is of less consequence than the reorganization of solvent about the forming anion. On the simplest solvation model the latter would lead to a more negative entropy for the isopropyl ester unless we invoke some opposing mechanism such as the depolymerization hypothesis of Frank and Evans, discussed in the previous section. A program of research to explore this possibility and to determine corresponding parameters in other series is now in progress.

n-Propyl Benzenesulphonate

The *n*-propyl benzenesulphonate was studied as an extension of an earlier examination of the effect of lengthening the alkyl chain in hydrolysis (23) and for comparison with the trends in heat capacity and entropy which characterize the dissociation of straight chain weak acids (8). The data in Tables VIII and IX show that while the addition of a β -methyl to ethyl results in but a small change in the rate compared to the second α -methyl, this small change is the result of larger compensating changes in the heat and

TABLE VIII
SUMMARY OF THERMODYNAMIC DIFFERENCES

$\Delta \Delta$	Methyl	Ethyl	Isopropyl	<i>n</i> -Propyl
$\Delta\Delta F^\ddagger_{298.16}$ cal.	0	-812	+1027	-784
$\Delta\Delta H^\ddagger_{298.16}$ cal.	0	+611	+384	+63
$\Delta\Delta C_p^\ddagger$ cal./mole deg.	0	-1.06	-7.79	+2.15
$-\Delta\Delta S^\ddagger$ cal./mole deg.	0	+1.78	+7.48	-0.56

TABLE IX

A COMPARISON OF RELATIVE RATES OF SOLVOLYSIS FOR A SERIES OF BENZENESULPHONIC ESTERS

Benzenesulphonate	Methyl	Ethyl	Isopropyl	<i>n</i> -Propyl	Isobutyl	Neopentyl
Ethanol*	1.0	0.45	1.45	0.26	0.023	0.00026
Water†	1.0	0.99	24.8	0.72	0.22	0.10
Acetic acid‡	1.0	0.9	—	—	0.28	0.10

*Ref. 28.

†Ref. 23 and this paper; temp. = 50° C.

‡Ref. 37.

entropy of activation. A similar reversal in trend is evident in the heat capacity change. In the dissociation of weak acids, the positive trend in heat capacity was attributed to a chain-stiffening effect resulting from exclusion by the solvent of the alkyl chain from the charge center. This may contribute to the present reversal, but other factors must be considered since the entropy shift found here is the opposite to that required by the chain-stiffening hypothesis.

CONCLUSION

We have considered the above esters to hydrolyze in water by an intermediate mechanism in which ionization forces are important. While nucleophilic attack by a solvent molecule has not been excluded by this study, arguments based on relative rates in solvents of varying nucleophilic and ionizing ability, on the small differences in the rates and derived thermodynamic parameters, and on the similarity between the values of ΔC_p for the ionization of weak acids and value of ΔC_p^\ddagger observed here all point to a mechanism which approaches an ionization in character. The changes in ΔS^\ddagger and ΔC_p^\ddagger have therefore been rationalized in terms of the reorientation of the solvent.

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REACTIONS OF ARYLSULPHONIC ESTERS

VII. THE HEAT CAPACITY OF ACTIVATION FOR THE ETHANOLYSIS OF METHYL *p*-NITROBENZENESULPHONATE¹

J. B. HYNE² AND R. E. ROBERTSON

ABSTRACT

A conductometric method is described for the determination of rates of solvolyses in non-aqueous media with an accuracy of better than $\pm 0.5\%$ in k . The heat of activation derived from the results so obtained is shown to have a temperature coefficient (ΔC_p^\ddagger) of -21 cal./mole deg.

The utility of the heat capacity of activation as a parameter in the study of reaction mechanisms in solution has already been noted (3, 4) and recently reported experimental work (7, 8) has established the practicability of such determinations. Previous work from this laboratory, however, has been restricted to hydrolysis reactions in water where the high degree of dissociation of the product acids permits a simplification of experimental method. The importance of solvent influence on reaction mechanism in solution made it desirable to extend the study of heat capacities of activation to non-aqueous systems. Such an extension raises many experimental problems. The accuracy required in rate measurements of solvolytic reaction for use in heat capacity computations can be most conveniently attained by conductometric methods. In aqueous solution many systems can be used where the product of the reaction is completely ionized and the conductivity over a considerable range is a linear function of the concentration to a sufficiently high degree of approximation. This is not true in non-aqueous systems, and a calibration technique is required for conversion of conductometric data to concentration units which can then be employed directly in the computation of rates. This additional step has been employed in several instances (1, 2) with a consequent loss in accuracy of rate determinations.

Shiner and Verbanic (10) have recently reported rate data in 90% ethanol-water mixtures determined by the direct conductometric method; these authors claim that the relationship between conductivity and concentration is sufficiently linear under the conditions employed to enable determination of rates reproducible to 0.5%. The relationship was established by "independent measurements" and while the validity of these measurements is not questioned, it is clear that the linearity of the relationship is critically dependent upon both the concentration range over which linearity was established and upon the specific nature of the electrolyte being produced. Shiner and Verbanic found, as we did, that there was no such linearity in pure ethanol and as a consequence did not use this solvent in their work. Since we were particularly interested in the magnitude and sign of the heat capacity of activation in pure solvents, particularly in the alcohol series, there was a need for a method utilizing the extreme accuracy of the conductometric system but capable of application to a wide range of non-aqueous media worthy of investigation.

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We describe the development of such a system in some detail and demonstrate its utility by determining the heat capacity of activation for the solvolysis of methyl *p*-nitrobenzenesulphonate in ethanol.

EXPERIMENTAL DETAIL

The basic requirement of the experimental technique is that the conductometric method employed be independent of degree of ionization of the ionic species being produced. This has been achieved by employing the conductivity as a null point indicator.

Two magnetically stirred conductivity cells (Fig. 1) of approximately 100 ml. volume containing identical solutions of the electrolyte to be produced in the reaction are totally immersed in a thermostat controlled to $\pm 0.003^\circ\text{C}$. (7). These cells (*cl*) constitute the two arms of a standard a-c. Wheatstone network (Fig. 2). After thermal equilibrium

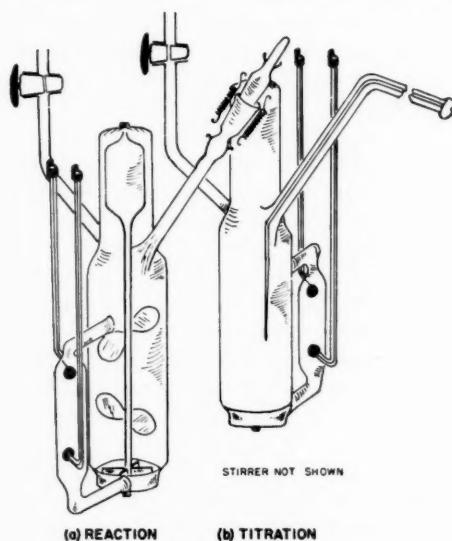


FIG. 1.

has been established, the bridge is balanced by adjustment of R_1 and R_2 , the compensating capacitors C_1 and C_2 , and the Wagner grounding circuit. Since the bridge is operated at all times as a null point instrument, stability is the only requirement and inexpensive components may be used. This balance point represents identical ionic concentrations in the two cells and compensates for any difference in the cell constants. The bridge setting remains unaltered throughout the course of any given run. The "titration cell" (Fig. 1, *b*) is connected through a fine capillary to a precision delivery titrimer and a concentrated solution of the electrolyte to be produced in the reaction is pumped from the titrimer to the cell. No change in the balance point of the bridge detector is noted until the solution reaches the stirred cell. At this point the titrimer reading is noted and represents zero volume delivered to the cell.

Approximately 10^{-4} moles of the material to be solvolyzed is now introduced into the "reaction cell" (Fig. 1, *a*) *in situ*. Production of the electrolyte by solvolysis immediately

affects the balance point of the bridge and can be followed qualitatively on the bridge detector. Electrolyte is now added from the titrimer to the titration cell to counter-balance that being produced in the reaction cell. Normally excess electrolyte is added to the titration cell and the reaction cell allowed to "catch up". When the original balance point is regained (equal ionic strengths), a time reading is taken corresponding to the titrimer reading minus the zero volume reading. Successive readings may be taken in a similar manner throughout the course of the reaction.

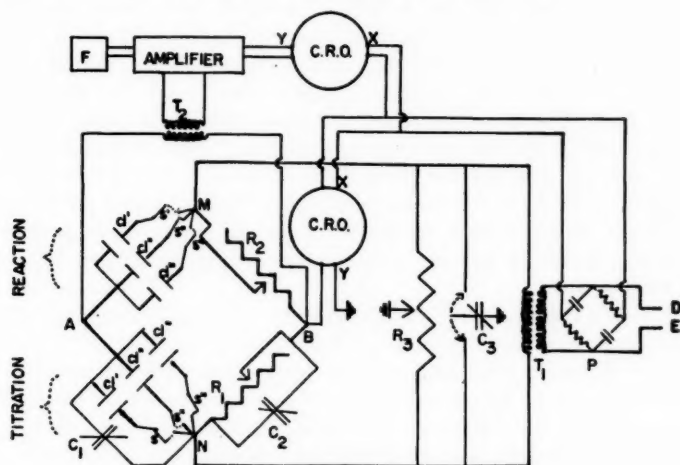


FIG. 2.

Comments on Method

(1) Since all readings are taken at identical concentrations in the two cells, changes in degree of ionization with concentration are equal in both arms of the bridge and consequently there is no net effect on the balance point of the bridge.

(2) It is essential that changes in concentration in the titration cell be a linear function of the titrimer scale reading, i.e., of volume delivered. This is not strictly the case since, while electrolyte is being produced in the reaction cell without significant change of volume, the change in electrolyte concentration in the titration cell is accompanied by a net change in total volume due to the volume delivered from the titrimer. A correction factor is, therefore, applied to the titrimer reading. This can be easily computed from the volume delivered to the cell at each reading and the original volume of solution in the cell. The factor may be kept small by using a concentrated solution of electrolyte in the titrimer; the total volume delivered to the cell will then be small—of the order of 3 to 5 ml. for the complete run.

(3) The more important technical difficulties which must be overcome are worthy of mention. (a) At higher temperatures with low boiling solvents back pressure in the delivery capillary can be troublesome. All joints must be liquid tight under pressure. This includes the capillary jointing and the piston seals in the titrimer. (b) Back diffusion of solution from the delivery tip in the titration cell can be overcome by adding electrolyte in slight excess *immediately prior* to the taking of the reading. Any diffusion that has taken place between readings will then be accounted for in the volume delivered.

(c) Care is essential in adding the reactant to the reaction cell. The tip of the delivery pipette must be inserted *under* the solvent level to ensure that no reactant adheres to the glass of the injection port and enters the solution *after* readings have begun. All but very insoluble reactants are homogeneously distributed by the stirrer within two to three minutes. (d) In view of the length of the delivery capillary unthermostated it was found desirable to limit fluctuation of the ambient room temperature throughout a given run to $\pm 1.0^\circ \text{C}$.

(4) The titrimer used in this work was a precision instrument constructed in the workshops of these laboratories and capable of delivering up to 10 ml. with an accuracy of ± 0.001 ml. The vertically mounted barrels were of Teflon and the pistons were precision ground from Hastelloy B alloy. Glass barrels were also used. Glands were fashioned from Teflon. The drive train from the electric motor to the pistons incorporated a three-speed gearbox mainly for convenience in flushing and recharging barrels between runs. With concentrated solutions of electrolytes in contact with the alloy pistons over long periods of time sufficient corrosion was observed to establish intolerable concentration gradients in the solution in the barrel. This was overcome with the electrolytes used by introducing sufficient mercury into the barrel to prevent direct contact between piston and electrolyte.

(5) In addition to achieving the high degree of accuracy attainable by use of the conductometric method without restriction to aqueous media this method also preserves the advantage of following the rates without interfering with the reacting system in any mechanical manner. In the present work it was unnecessary to calibrate the titrimer units in terms of concentration as the rate constants measured were independent of concentration units. In the many studies where changes in concentration units are required, however, simple calibration would render this instrument a useful experimental tool.

COMPARISON WITH OTHER METHODS

Robertson (7) has reported rates of hydrolysis of methyl benzenesulphonate over a wide range of temperatures using a well established direct conductometric method. From this work the value $k = 31.85 \times 10^{-5}(\text{sec.}^{-1})$ at 54.790°C . can be computed. This system was run in the present apparatus for comparison and a value of $31.84(\pm 0.03) \times 10^{-5}(\text{sec.}^{-1})$ was obtained.

Robertson (9) has previously reported the rate of ethanolysis of methyl *p*-nitrobenzenesulphonate at 70°C ., determined by a simple aliquot and titration technique, as $k = 65.3(\pm 0.7) \times 10^{-5}(\text{sec.}^{-1})$ compared with the value obtained in this work $k = 64.53(\pm 0.1) \times 10^{-5}(\text{sec.}^{-1})$.

RESULTS

A typical solvolytic rate determination in non-aqueous medium, the ethanolysis of methyl *p*-nitrobenzenesulphonate, is shown below. Typical rate plots (Fig. 3) and preparative data are recorded for a determination at 60°C . and rate data for this solvolysis from 40°C . to 75°C . are shown in Table I.

Typical Experiment at 60°C .

Preparative

Methyl *p*-nitrobenzenesulphonate synthesized by the method of Morgan and Cretcher (6) from Eastman White Label *p*-nitrobenzenesulphonyl chloride. Recrystallized from 60–80 petroleum ether to m.p. 53°C . Absolute ethanol dried by the diphthalate method.

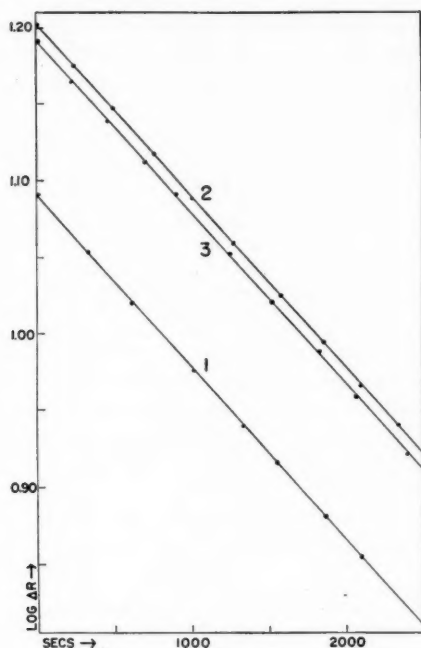


FIG. 3.

TABLE I
RATES OF ETHANOLYSIS OF METHYL *p*-NITROBENZENESULPHONATE
FROM 40° C. TO 75° C.

Temperature, ° C.	$k(\text{sec.}^{-1}) \times 10^5$ (obs.)	$k(\text{sec.}^{-1}) \times 10^5$ (calc.)*
40.000	3.50	3.497
43.295	4.97 ⁰	4.966
47.380	7.55 ¹	7.585
50.000	9.93	9.886
54.997	16.1 ²	16.17
60.001	25.8 ⁷	26.05
62.300	32.3 ¹	32.20
66.370	46.6 ⁶	46.57
67.515	51.5 ⁵	51.58
70.002	64.5 ³	64.20
72.295	77.9 ⁵	78.29
75.001	98.5 ⁵	98.58

*Computed from equation relating k and T using A , B , C values of Table II.

Solutions

Backing electrolyte—0.001 *M* *p*-nitrobenzenesulphonic acid in ethanol; titrating electrolyte—0.02 *M* *p*-nitrobenzenesulphonic acid in ethanol; reactant added—0.01 g. methyl *p*-nitrobenzenesulphonate in 1 ml. ethanol.

Guggenheim rate plots for three determinations at 60° C. are shown in Fig. 3. Rates determined from large scale plots were (1) 25.96×10^{-5} , (2) 25.89×10^{-5} , (3) 25.77×10^{-5} sec.⁻¹. This represents a reproducibility of $\pm 0.4\%$ in k comparable with the precision of individual rate determinations.

From the data of Table I values of the constants for the equation (3, 7)

$$\log_{10} k = A/T + B \log_{10} T + C$$

are evaluated by the method of least mean squares. These values are shown in Table II

TABLE II
THERMODYNAMIC CONSTANTS FOR ACTIVATION AND
EQUATION CONSTANTS

A	$= -5885.3$
B	$= -9.5471$
C	$= +38.1643$
$\Delta F^\ddagger_{298.15}$	$= +24,557$ cal./mole
$\Delta H^\ddagger_{298.15}$	$= +20,708$ cal./mole
$\Delta S^\ddagger_{298.15}$	$= -12.79$ e.u.
ΔC_p^\ddagger	$= -20.96 \pm 3.5$ cal./mole deg.

together with the thermodynamic constants for the activation process. These latter can be calculated by identifying A , B , and C with the coefficients of the expanded form of the Eyring equation,

$$\log_{10} k = -\Delta H_0^\ddagger/2.303 RT + (\Delta C_p^\ddagger/R + 1) \log_{10} T + [(\Delta S_0^\ddagger - \Delta C_p^\ddagger)/2.303 R + \log_{10} k/h].$$

The error for ΔC_p is computed from the standard error in coefficient B obtained from the least mean square calculation. The higher error, compared with other data reported from this laboratory, results largely from the smaller temperature range over which the rates were determined.

DISCUSSION

The primary purpose of this investigation was to develop a technique by which we might fully utilize the convenience and precision of the conductometric method in the study of solvolysis in non-aqueous media and thus to determine the respective heat capacities of activation. We believe this aim has been achieved although there are many refinements in the technique yet to be developed, in particular the extension of the temperature range and the attendant problem of back pressure in the system at higher temperatures. It was primarily to avoid this problem that the system methyl *p*-nitrobenzenesulphonate ethanolysis was chosen, since this solvolysis proceeds at a convenient rate at easily accessible temperatures.

The values of the thermodynamic parameters obtained in this initial investigation in non-aqueous medium are, nevertheless, of considerable interest. Clearly the value of the heat capacity of activation is lower than those values already reported (7, 8) for similar systems in water and for the methyl halide hydrolyses (5). It would appear, therefore, as hoped, that the heat capacity of activation is a parameter which shows considerable response to the solvent changes in the system.

Preliminary investigation of the thermodynamic parameters of activation for the methyl *p*-nitrobenzenesulphonate hydrolysis indicates that the ΔC_p^\ddagger value is in the region -26 to -27 cal./mole deg. which is considerably lower than that for the unsubstituted methyl benzenesulphonate hydrolysis ($\Delta C_p^\ddagger = -33.4$). Interpretation of the value for the *p*-nitro compound ethanolysis ($\Delta C_p^\ddagger = -21$) would, therefore, appear

to be dependent upon a twofold reducing effect relative to the unsubstituted case, the influence of the *p*-nitro group, and the effect of changing the solvent medium. The influence of changing the alkyl group on ΔC_p^\ddagger has already been observed (9) and it would now appear that variation of substituent on the aromatic anionic fragment is also reflected in the heat capacity change.

More detailed interpretation of the thermodynamic parameters obtained in this work must await further, more exhaustive study of similar systems. This investigation, however, establishes the fact that not only is the method described practical but that the heat capacity of activation has considerable merit as a measurable parameter in the study of solvent effects in non-aqueous as well as aqueous systems.

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THE DIPOLE MOMENTS OF MERCURIC CHLORIDE AND MERCURIC BROMIDE IN BENZENE¹

A. R. TOURKY AND H. A. RIZK

ABSTRACT

From dielectric constant measurements in benzene for the two halides mercuric chloride and mercuric bromide, the dipole moments are 1.23 and 0.95 D. respectively. Thus, they apparently possess angular structures.

Kohlrausch (18) gathered from Raman spectral data that mercuric chloride and mercuric bromide might possess linear structures. Bell (3) calculated the moments of these halides from solubility data and the values he obtained were 4.0 and 5.7×10^{-18} e.s.u. cm. respectively. Braekken and Scholten (5) concluded afterwards from X-ray analysis that the molecular configuration of mercuric chloride was linear, whereas that of mercuric bromide was not. Curran and Wenzke (8) determined the dipole moments of these two halides from dielectric constant measurements in dioxane on the opinion that these halides do not form co-ordination compounds with dioxane supported by the experimental fact that diphenyl mercury has the same dipole moment in dioxane as that determined by Hampson (12) in benzene and decalin. This conclusion was criticized by Crenshaw *et al.* (7), who found from vapor pressure measurements that mercuric halides form dioxanates in dioxane solutions. Williams (28) pointed out that the use of dioxane as a solvent in dipole moment studies is limited to compounds with which it does not form addition products. Curran, in an investigation concerning the dipole moments of some organomercuric halides in dioxane (9), concluded that if co-ordination between the dioxane and the mercuric halides took place, a coplanar configuration of the

type $^+\text{O}-\text{Hg} \begin{array}{l} \diagup \text{Cl} \\ \diagdown \text{Cl} \end{array}$ for mercuric chloride dioxanate with 120° valence angles would have resulted. This complex would have a moment greater than 5 D. The bromide and the iodide dioxanates would have slightly smaller moments. He thus postulated that dioxane does not form co-ordinated bonds with mercuric halides or organomercuric halides but forms dipole-dipole bonds between oxygen and mercury similar to the ion-dipole bonds between oxygen and metal cations in hydrates. In the present investigation, we have been able to study the polarization of mercuric chloride and mercuric bromide in benzene as a solvent. However, in view of the limited solubility of these compounds in benzene, the measurements could not be extended over a wide range of concentration.

EXPERIMENTAL

Mercuric chloride of "AnalaR" grade was crystallized three times from twice redistilled water and the product was dried first at 100°C . in a stream of dry air and then under vacuum. The chloride was finally distilled under vacuum. The crystals obtained were white, long-needed, and completely soluble in water. Mercuric bromide was synthesized according to the method of Baker and Watson (2). The product obtained was distilled under vacuum, thus producing pure white crystals. Benzene of grade "AnalaR", carbon tetrachloride, and nitrobenzene were rigorously dried and purified according to recommended procedures (27).

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The dielectric constant, ϵ , was measured using a resonance circuit in which a frequency of 1.875×10^6 c.p.s. was fixed by a quartz crystal. A specially designed cylindrical platinum cell was used instead of the silvered Sayce-Briscoe cell (25), as in the latter cell chemical interaction with the halides takes place. The measuring cell was rigidly fixed in a jacket that could be connected to an ultrathermostat. The air capacity of the cell was $30 \mu\text{f.}$, the range over which ϵ could be measured was 1.9 to 3.1, and the volume required to fill the annulus was 8 cc. For the calibration of the apparatus, liquids of reliable dielectric constants were used:

	Benzene (13, 19)	Carbon tetrachloride (19)	Nitrobenzene in benzene (17, 20)		
ϵ at 25°C.	2.2725	2.2270	2.2925	2.3000	2.3325
			$f_2 = 0.0008707$	0.001197	0.002612

The uncertainty in ϵ was ± 0.0005 . The density was measured by a pycnometer of the Sprengel-Ostwald type that was filled by the method of Smyth and Morgan (26) and Miller (23). The pycnometer was first calibrated using carbon-dioxide-free redistilled water, and the density of the liquid was corrected for the buoyancy of air. The refractive index for the sodium D line was measured directly by means of a Hilger-Abbé refractometer. The composition of the solutions in weight fraction was determined using the Eley and King method (11). The temperature at which measurements were carried out was $25^\circ \pm 0.002^\circ \text{C.}$

RESULTS AND DISCUSSION

The total specific polarization of each halide, p_2 , at different concentrations in benzene was calculated from the modified Clausius-Mosotti-Debye equation applicable to solutions (6, 10). The polarization at infinite dilution, $p_{2\infty}$, was graphically and mathematically determined. In the latter case the Hedestrand method (14) and the Palit-Banerjee method (24) were used. To get the best values of $p_{2\infty}$ the method of least squares was applied; the mean of the values obtained was then taken. The part of the molecular polarization arising from the induced dipoles was calculated from measurements of the refractive index for the sodium D line using the modified form of the Lorenz-Lorentz equation applicable to solutions (21). The molecular refraction was then corrected by applying the dispersion formula $(1 - \lambda_0^2/\lambda^2)R_2$, where $\lambda_0 = 1013 \text{ \AA}$ (23) and $\lambda = 5896 \text{ \AA}$ (1), so as to get the molecular refraction for infinite wave-length, $R_{2\infty}$, which is identical with the electronic polarization, ${}_EP_2$. The deformation polarization, ${}_DP_2$, was taken as $1.10R_{2\infty}$ (29) and the apparent dipole moment, μ , was calculated by the refractivity method. The data obtained are shown in Tables I and II.

It can be seen from these tables that the electronic polarizations of mercuric chloride and mercuric bromide for infinite wave-length, namely 29.65 and 54.99 cc., are lower than the values, 30.36 and 55.30 cc., which were obtained by Bergmann and Engel (4) and applied by Curran and Wenzke (8) by 0.71 and 0.31 cc. respectively. The magnitude of the orientation polarization of mercuric chloride which has been applied in calculating the dipole moment is 21.36 cc., being taken as the difference between the total polarization, 63.97 cc., and 1.10 times the electronic polarization for infinite wave-length, 32.61 cc. On the other hand, Curran and Wenzke's value (8) is $65.03 - 30.36 = 24.67$ cc. The same can be said with regard to mercuric bromide; our orientation term is $79.03 - 60.49 = 18.54$ cc., whereas that given by Curran and Wenzke (8) is $78.63 - 55.30 = 23.33$ cc. It is thus evident that the polarization values of these two halides taking benzene as the

TABLE I
MERCURIC CHLORIDE IN BENZENE
(Temp. 25° C.)

w_2	ϵ_{12}	d_{12}	n_{12-D}	p_{12} (cc.)	p_2 (cc.)	r_{2-D} (cc.)
0	2.2725	0.87391	1.4933			
0.0005755	2.2735	0.87455	1.4935	0.34076	0.23657	0.10685
0.001902	2.2760	0.87608	1.4940	0.34062	0.23567	0.11192
0.003299	2.2785	0.87766	1.4946	0.34047	0.23473	0.11147
0.004759	2.2810	0.87932	1.4951	0.34030	0.23156	0.11421
$M_2 = 271.52$, $\epsilon_{12} = \epsilon_1 + \alpha w_2$, $d_{12} = d_1 + \beta w_2$, $p_{12} = A + \gamma w_2$ $\alpha = 1.8004$, $\beta = 1.1369$, $A = 0.34082$, $\gamma = -0.10791$ $p_{2cc}(\text{graph.}) = 0.2379$, $p_{2cc}(\text{Hedestrand}) = 0.23605$, $p_{2cc}(\text{Palit-Banerjee}) = 0.23291$ $P_{2cc} = 64.59$, $P_{2cc} = 64.09$, $P_{2cc} = 63.97$ $P_{2cc} = 63.97$ $r_{2-D} = 0.11254$, $R_{2-D} = 30.55$, $E P_2 = R_{2cc} = 29.65$, $D P_2 = 32.61$ $\mu = 1.23$ D.						

TABLE II
MERCURIC BROMIDE IN BENZENE
(Temp. 25° C.)

w_2	ϵ_{12}	d_{12}	n_{12-D}	p_{12} (cc.)	p_2 (cc.)	r_{2-D} (cc.)
0	2.2725	0.87391	1.4933			
0.0005714	2.2735	0.87456	1.4936	0.34075	0.21831	0.15773
0.001380	2.2750	0.87552	1.4940	0.34065	0.21763	0.15883
0.001690	2.2755	0.87586	1.4941	0.34061	0.21656	0.15523
0.002341	2.2765	0.87659	1.4944	0.34053	0.21694	0.15760
$M_2 = 360.44$, $\epsilon_{12} = \epsilon_1 + \alpha w_2$, $d_{12} = d_1 + \beta w_2$, $p_{12} = A + \gamma w_2$ $\alpha = 1.7465$, $\beta = 1.1510$, $A = 0.34082$, $\gamma = -0.12345$ $p_{2cc}(\text{graph.}) = 0.2200$, $p_{2cc}(\text{Hedestrand}) = 0.22041$, $p_{2cc}(\text{Palit-Banerjee}) = 0.21737$ $P_{2cc} = 79.30$, $P_{2cc} = 79.44$, $P_{2cc} = 78.35$ $P_{2cc} = 79.03$ $r_{2-D} = 0.15722$, $R_{2-D} = 56.67$, $E P_2 = R_{2cc} = 54.99$, $D P_2 = 60.49$ $\mu = 0.95$ D.						

solvent are in agreement with the values obtained by Curran and Wenzke (8) using dioxane. The dipole moment values are 1.23 and 0.95 D. for mercuric chloride and mercuric bromide respectively, whereas those due to Curran and Wenzke (8) are 1.29 and 1.06 D. respectively.

The polarities of these two halides indicate that they possess dissymmetric distribution of charges. Whether the dissymmetry is ascribable to a bent structure or to dissimilar distances of the halogen nuclei from the mercury in a linear molecule must be decided by other measurements. With respect to this point reference can be made to the water molecule, which resembles mercuric halides, being of the type structure XY_2 and having a finite dipole moment value. The rotation spectrum of water as determined by Mecke (22) and the theoretical considerations of Heisenberg (15) and of Hund (16) necessitate a bent structure and not a linear one. Thus, it seems very likely that mercuric chloride and bromide molecules are of angular structures. The decrease in the electric moment from 1.23 to 0.95 D. as we pass from the chloride to the bromide indicates a decrease in the dissymmetry of the charge of the $Hg-X$ bond along the direction of the bond. This can be attributed to the fact that as the electron cloud in the bromide ion is greater than that in the chloride ion, then the induced moment $Hg \leftarrow X$ which opposes the permanent moment will increase to an extent greater than the increase in the permanent moment

due to the increase in the nuclear distance. The decrease in polarity may be also partly ascribed to an increase in the valency angle as a result of the greater repulsion between the two bromide ions; but in order that this view be fully justified, other types of measurements than the dipole moment measurements are needed.

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THE HEMICELLULOSES PRESENT IN ASPEN WOOD (POPULUS TREMULOIDES)

PART III. THE CONSTITUTION OF PENTOSAN AND HEXOSAN FRACTIONS¹

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ABSTRACT

Extractive-free aspen wood (*Populus tremuloides*) was extracted with water, followed by alkaline solutions of successively increasing concentration, and finally with alkaline borate solution. Hemicellulose fractions (I-IX) were thus obtained, and some of these were further subdivided into components which formed water-insoluble copper complexes (A) and those which did not (B). Analytical data are recorded for each fraction.

One of the fractions (V) represented 19% by weight of the original wood. Hydrolysis of the methylated material gave 2,3,5-tri-*O*-methyl-L-arabinose, 2,3,4-tri-*O*-methyl-D-xylose, 2,3-di-*O*-methyl-D-xylose, 2- and 3-mono-*O*-methyl-D-xyloses, and three acidic fragments as the major components.

When V was treated with an enzyme preparation, 80% by weight of the material was hydrolyzed to simple sugars, and an enzyme-resistant polysaccharide fraction remained. Methylation of the latter, followed by hydrolysis, afforded, in addition to those methylated sugars described above, 2,3,4,6-tetra-*O*-methyl-D-mannose.

A mannose-rich hemicellulose fraction (VIII A) was also methylated and then hydrolyzed. The major products were 2,3,4,6-tetra-*O*-methyl-D-mannose, 2,3,6-tri-*O*-methyl-D-mannose, and 2,3,6-tri-*O*-methyl-D-glucose. The significance of these results is discussed.

INTRODUCTION

In Parts I and II of this series of papers, the hemicellulosic fraction of aspen wood was studied by controlled acid hydrolysis of the crude wood (7, 8). The major products of hydrolysis were shown to be the monosaccharides L-rhamnose, L-arabinose, D-xylose, D-galactose, and 4-*O*-methyl-D-glucuronic acid. In addition, three oligosaccharides, a xylobiose, a xylotriose, and 2-*O*-(4-*O*-methyl- α -D-glucuronosyl)-D-xylose were identified. Since then, Milks and Purves (11) have studied aspen holocellulose by treatment of the wood with wet liquid ammonia, followed by acetylation of the extracted material. Methylation of the acetate, followed by hydrolysis, led to the isolation of 2,3-di-*O*-methyl-D-xylose, and a mixture of 2- and 3-mono-*O*-methyl-D-xyloses.

In the present work, an attempt has been made to fractionate the total carbohydrate fraction of aspen wood. The crude, extractive-free wood was extracted first with cold water, from which a polysaccharide fraction (I) was isolated. Stepwise extraction of the residue with potassium hydroxide solutions of successively increasing concentration then led to the isolation of five hemicellulose fractions (II-VI). Extraction of the residue with alkaline borate solution (9) gave a solution, neutralization of which resulted in the precipitation of another hemicellulose fraction (VII). From the supernatant solution, a further hemicellulose fraction (VIII) was isolated.

The woody residue was then delignified by the method of Wise, Murphy, and D'Addieco (14). By extraction of the remaining material with alkaline borate solution, the former was divided into a hemicellulose fraction (IX) and a cellulose-rich residue.

Each of fractions I-V was hydrolyzed. Chromatographic examination of the products indicated that the major component in each case was xylose, together with smaller amounts of arabinose, glucose, mannose, galactose, rhamnose, fucose, and uronic acids.

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Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario, and the Institute of Paper Chemistry, Appleton, Wisconsin, U.S.A. This paper represents part of a thesis submitted by E. Merler to the Department of Chemistry, Queen's University, Kingston, Ontario, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

When fractions I-V were subdivided into copper complexing (A) and non copper complexing (B) subfractions, each subfraction was similarly shown to contain the same sugar residues as above, in varying amounts. The fractions and subfractions were analyzed for methoxyl and uronic anhydride content. The results are collected in Table I.

Fraction V represented 19% by weight of the original wood. When subjected to electrophoresis on sheets of glass paper (2), it was shown to be resolvable into two major components. Furthermore, when this fraction was treated with a special enzyme preparation, it was hydrolyzed to the extent of 80%; the remaining 20% represented an enzyme-resistant polysaccharide fraction. When the latter was examined by glass paper electrophoresis, it was observed that one of the original components had largely disappeared. It was therefore considered to be of interest to examine both the original material and the enzyme-resistant material by methylation techniques. Fraction V contained xylose (67 parts), arabinose (2 parts), rhamnose (3 parts), hexoses (2 parts), and uronic anhydride (9 parts) (6) in the proportions indicated. On methylation, followed by hydrolysis, it gave 2,3,5-tri-*O*-methyl-L-arabinose (1 part), 2,3,4-tri-*O*-methyl-D-xylose (1 part), 2,3-di-*O*-methyl-D-xylose (210 parts), 2- and 3-mono-*O*-methyl-D-xyloses (3 parts), and uronic acid fragments (20 parts), together with traces of an unidentified tri-*O*-methyl-hexose (3 parts).

The enzyme-resistant polysaccharide contained xylose (74 parts), arabinose (6 parts), rhamnose (2 parts), hexoses (2 parts), and uronic anhydride (4 parts) (6) in the proportions indicated. Hydrolysis of the methylated material afforded 2,3,5-tri-*O*-methyl-L-arabinose (1 part), 2,3,4-tri-*O*-methyl-D-xylose (1 part), 2,3-di-*O*-methyl-D-xylose (270 parts), 2- and 3-mono-*O*-methyl-D-xyloses (4 parts), and three uronic acid fragments (33 parts), together with traces of 2,3,4,6-tetra-*O*-methyl-D-mannose and 2,3,4-tri-*O*-methyl-L-arabinose. Owing to the difficulties in the fractionations of the sugars losses occurred, particularly of the more volatile portions, and for this reason the proportions quoted are approximate only.

The neutral methylated sugars were all characterized either as the crystalline compounds, or as crystalline derivatives of the compounds. The uronic acid fractions in each case were not easily resolvable by chromatographic means. The mixtures were therefore treated with hot methanolic hydrogen chloride to convert the sugars into their methyl esters and methyl glycosides, and the products reduced with potassium borohydride (10). Hydrolysis of the resulting sirupy materials in each case gave a mixture of 2,3,4-tri-*O*-methyl-D-glucose and 2,3,6-tri-*O*-methyl-D-glucose which were provisionally identified from a study of the derivatives produced after reduction followed by periodate oxidation of the resultant sugar alcohols. 3,4-Di-*O*-methyl-D-xylose was identified by converting it to 3,4-di-*O*-methyl-D-xylonolactone, and 2- and 3-mono-*O*-methyl-D-xyloses were tentatively identified by means of paper electrophoresis.

The hemicellulose fractions VI-IX were all relatively rich in hexose residues, the principal hexose being mannose, as indicated by chromatographic examination of the hydrolyzed materials. Fraction VIII was especially rich in mannose residues, and after formation of a copper complex, a fraction (VIII A) was isolated which contained residues of D-mannose (18 parts), D-glucose (9 parts), and D-xylose (1 part). Methylation of this fraction, followed by hydrolysis, gave rise to 2,3,4,6-tetra-*O*-methyl-D-mannose (2 parts), 2,3,6-tri-*O*-methyl-D-mannose (24 parts), and 2,3,6-tri-*O*-methyl-D-glucose (12 parts), identified by means of crystalline derivatives and in the approximate proportions indicated. Also, evidence was obtained for the presence of small amounts of 3,4,6-

tri-*O*-methyl-D-mannose, 2,3-di-*O*-methyl-D-xylose, and 2,6-di-*O*-methyl-D-glucose in the hydrolyzate.

From the above work it would appear that the pentosan fraction of aspen wood contains a mixture of polysaccharides which are very similar in their general architecture, this similarity being sufficient to prevent any sharp fractionation into chemically distinct molecular species. The fact that fractionations which are dependent upon the solubility of the polysaccharides, or of their copper complexes, failed to give fractions differing in the kind of sugar residue present implies that the pentosans are highly heterogeneous in both the physical and chemical sense. It may be noted that the xylans from the hardwoods beech (1) and birch (12) are long-chain molecules while that from the softwood western hemlock (3) is highly branched. The latter concept appears to be the most probable explanation for the behavior of the enzyme preparation, since the enzyme-resistant polysaccharide isolated from fraction V contained less than half the uronic acid of the original and three times the arabinose. However, in the absence of knowledge of the exact specificity of the enzymes, it is not possible to draw any positive conclusions. Fractions I-III were totally resistant to enzymic attack, perhaps because they contained acetyl groups, but fraction IV was completely hydrolyzed by the enzyme.

Although the fine structures of the xylans remain obscure, it is clear that they all contain chains of (1 → 4) linked xylose residues, to which are attached, through positions 2 and 3 of a xylose residue, occasional end groups of L-arabofuranose residues and side chains which are terminated by uronic acid residues. It is uncertain whether residues of mannose or rhamnose are incorporated in this structure, or, if they are, by what kind of linkage. The nature of the uronic acid end groups presents an interesting problem. The enzymic hydrolyzate of fraction V was shown to contain 4-*O*-methyl-D-glucuronic acid. The uronic acid fraction isolated after hydrolysis of the methylated xylans, after treatment with methanolic hydrogen chloride followed by reduction, gave a product which was hydrolyzed to yield a mixture of 2,3,4- and 2,3,6-tri-*O*-methyl-D-glucoses. The former probably resulted principally from glucuronic acid or 4-*O*-methyl glucuronic acid residues in the original polysaccharide. The latter must have resulted from neutral glucose residues, which were probably intermediate between a uronic acid end group and a xylose residue. The isolation of 3,4-di-*O*-methyl-D-xylose from the hydrolyzate would suggest that xylose residues are also incorporated in the side chains.

The structure of the glucomannan fraction (VIII A) is less complex. It appears to contain essentially (1 → 4) linked chains of glucose and mannose residues; the non-reducing end groups are mainly mannose residues. Alternatively, this fraction could be a mixture of a (1 → 4) linked mannan and a similarly-linked glucan. While this fraction represents only a small part of the total hemicellulosic fraction of the wood (*ca.* 2%), it is interesting that it resembles the glucomannans which have been found in some softwoods. The xylose residues probably arise from a contaminating xylan. The origin of the 3,4,6-tri-*O*-methyl-D-mannose and 2,6-di-*O*-methyl-D-glucose produced on hydrolysis of the methylated glucomannan fraction is not clear.

All efforts to obtain a residual cellulose which would give only glucose on hydrolysis were unsuccessful. Traces of xylose and mannose were always detected in the hydrolysis products of the residual α -cellulose. However, the amounts of foreign sugars percentage-wise formed on hydrolysis of the α -cellulose were very small. Much further work will be required before it is decided whether these sugars form part of the cellulose molecule or whether they arise from associated xylan and mannan.

EXPERIMENTAL

Paper partition chromatography was carried out on Whatman No. 1 filter paper, with the upper layers of the following solvent systems (v:v): (A) *n*-butanol-ethanol-water-ammonia (4:1:4.9:0.1); (B) benzene-ethanol-water (169:47:15); (C) *n*-butanol-pyridine-water-benzene (5:3:3:1); and with the systems (D) *n*-butanol-pyridine-water (10:3:3); (E) ethyl acetate - acetic acid - formic acid - water (18:3:1:4). Solvents were removed under reduced pressure and at ca. 40° C.

Extraction and Fractionation of the Hemicelluloses

Milled aspen wood (370 g.), as received from The Institute of Paper Chemistry, Appleton, Wisconsin, was washed continuously by percolation with the azeotrope of benzene and ethanol. The extractive-free plant tissue (350 g.) was evenly packed in a column, and tap water (30 liters) was percolated slowly through the material until a small sample gave a nearly negative Molisch test. This water extract was concentrated to a small volume which was poured into ethanol containing hydrochloric acid (1% of concentrated acid); the precipitate was redissolved in water and reprecipitated with ethanol, washed with ether, and dried (fraction 1: 7.8 g., 2.1%). The residual plant tissue was extracted with aqueous potassium hydroxide (1%). A portion of this solution was neutralized on contact with the wood; this neutral solution was concentrated, and the concentrate poured into alcoholic-hydrochloric acid (as above) to give fraction 2 (1.8 g., 0.5%). After percolation the alkaline solution was acidified with acetic acid and the precipitate collected at the centrifuge (fraction 3: 2.0 g., 0.5%). The supernatant liquid from fraction 3 was concentrated and the residue poured into alcoholic-hydrochloric acid. The precipitate was redissolved in water and precipitated again with ethanol (fraction 4: 13.6 g., 3.7%). These alkaline extractions of the woody tissue were continued, using successively 10% and 20% potassium hydroxide, and gave respectively fraction 5 (70.0 g., 19%) and fraction 6 (7.8 g., 2.1%).

Fractions 1, 2, 3, 4, and 5 were further subdivided into subfractions *A* and *B* by adding Fehling's solution to solutions of the polysaccharides. Subfractions *A* represent the materials forming insoluble copper-complexes and *B* the materials not forming copper-complexes. The recoveries of material in these experiments ranged from 60% to 85%. Fraction 6 was not investigated further. Altogether 14 fractions were obtained; each, when hydrolyzed, gave mainly xylose with smaller amounts of arabinose, rhamnose, uronic acids, and at least one of the hexoses glucose, mannose, and galactose. The fractions soluble in water also contained small amounts of a sugar moving chromatographically at the same rate as fucose; galactose concentrated in subfractions *B* and fucose in subfractions *A*. Physical constants of the fractions are recorded in Table I. The uronic acid content was estimated on the basis of carbon dioxide formed on heating the polysaccharide with hydrochloric acid (12%) (6). Optical rotations were determined in sodium hydroxide solution (*N*):

Extraction and Fractionation of the Woody Residue after the Previous Extractions

The residue (300 g.), which was rich in cellulose and lignin, was stirred for 72 hours with a solution of potassium hydroxide - borate (2.5 liters, 20:4%) (9). The mixture was filtered through a medium sintered-glass funnel, the filtrate was neutralized with acetic acid, and the woody residue was extracted twice more. The combined neutralized filtrates were dialyzed and the solid which precipitated was removed at the centrifuge (fraction 7: 1.2 g., 0.4%). The supernatant liquid (10 liters) was concentrated and the residue

TABLE I
 PHYSICAL CONSTANTS OF ASPEN WOOD FRACTIONS

Fraction	$[\alpha]_D^{25} (c, 1.0)$	Methoxyl, %	Uronic anhydride, %
1	-1	3.4	20.3; 20.1
1A	+2	3.4	21.9
1B	-3	5.2; 5.2	23.0
2	-18	3.6; 3.4	11.2; 11.8
2B	-18	2.3; 2.2	11.2
3	-4	6.7; 6.8	7.6; 7.4
3A	-10	5.0; 5.6	7.5
3B	+15	1.9; 2.1	0.9
4	-63	1.6; 1.7	5.0; 5.2
4A	-73	1.8	4.2
4B	-48	1.8	7.9
5	-75	1.7; 1.7	9.3; 9.1
5A	-79	1.7	8.5
5B	-74	1.3	4.5

(200 ml.) poured into ethanol (1 liter) to which concentrated hydrochloric acid (10 ml.) had been added. After reprecipitation the material was dried (fraction 8: 3.8 g., 1.2%). The woody residue from the above treatment was delignified by the chlorite method (14) and the residue was shaken overnight with cuprammonium hydroxide (13). The undissolved material was removed at the centrifuge and the ammoniacal supernatant solution was neutralized with hydrochloric acid. The precipitate which formed was separated (centrifuge) and treated at room temperature with the potassium hydroxide - borate solution for 100 hours. The polysaccharide in the extract was isolated as described above. A portion of the residual cellulose (25 g.) was added to sulphuric acid (20 ml., 72%); initially the temperature of the reaction was kept below 10° C. After 12 hours, water was added (1.5 liters) and the solution was heated on the boiling water bath for 24 hours. The solution was cooled and neutralized with barium hydroxide. The barium salts were removed at the centrifuge and the solution concentrated. The residue was composed mainly of glucose, but occurring also were mannose, xylose, and uronic acid residues as indicated by paper chromatography. (The yields are calculated on the basis of non-extracted wood.)

Fraction 8 (9.2 g., 3.0%) was dissolved in sodium hydroxide (2 *N*) and treated with a slight excess of Fehling's solution. This yielded a copper complex (8A), the supernatant liquid from which gave a precipitate with aqueous acetone (50%). Some polysaccharide remained in solution. With the exception of fraction 8A the various polysaccharides were tested for sugar units after hydrolysis, and were shown to contain varying amounts of all, or some, of the following: mannose, glucose, galactose, xylose, arabinose, fucose, rhamnose, and uronic acids. Fraction 8A (further treatment of which is given below) when hydrolyzed gave largely mannose and glucose with smaller amounts of xylose and uronic acids.

Properties of the Hemicellulose in Fraction 5 (Termed "Xylan")

Hydrolysis of fraction 5 (cf. Table I) with sulphuric acid (*N*) in a boiling water bath

for 12 hours and estimation of the liberated aldoses by the method of Hirst and Jones (4) indicated the presence of the following sugars (calculated as proportions of sugar in residues in the original xylan): xylose, 67 parts; arabinose, 2 parts; hexoses, 2 parts; and rhamnose, 3 parts. The lignin content (13, p. 369) was 3.4%.

Methylation of the Xylan

The xylan (10 g.) was methylated five times with methyl sulphate and sodium hydroxide. The reaction mixture was carefully acidified and extracted with chloroform to give an oil which solidified (10 g.). The material soluble in chloroform - light petroleum (b.p. 60-80° C.) (3:7) was isolated (7.2 g.), and a portion (5 g.) methylated four more times with methyl sulphate and sodium hydroxide. The methylated polysaccharide (3.3 g.) had $[\alpha]_D^{25} - 58^\circ$ (c , 1.5 in CHCl_3 ; found: OMe, 37.5%).

Hydrolysis of the Methylated Xylan and Identification of the Neutral Sugars

The methylated xylan (3.0 g.) was dissolved in aqueous formic acid (40 ml., 50%) and heated in a boiling water bath for 6 hours to constant optical rotation. The solution was cooled and concentrated to a sirup, which was dissolved in sulphuric acid (30 ml., N) and heated 3 hours on the boiling water bath until the solution had a constant optical rotation. The cooled solution was extracted continuously with chloroform for 2 days. The aqueous layer was neutralized with barium carbonate, the barium salts were removed at the centrifuge and washed with water, and the solvent removed. Since both the chloroform extract and the water fraction contained uronic acid residues (paper chromatography), the two samples were combined and cations were removed by passage through a column of Amberlite IR-120 (acid form) resin. The residue was separated in two portions by chromatography on a column of Amberlite IR-4B (acetate form) resin; thus a neutral fraction (2.311 g.) and an acidic fraction (0.232 g.) were obtained.

The neutral methylated sugars (2.311 g.) were separated into five fractions by partition chromatography on columns of cellulose powder (5), using as eluants light petroleum (b.p. 100-120° C.) - n -butanol (7:3) saturated with water, changing to light petroleum - n -butanol (6:4) saturated with water, than n -butanol saturated with water, and finally water. A part of this chromatographic separation was also made on extractive-free Whatman 3 MM paper. The full details of these separations are omitted because the operations were repeated many times to obtain pure fractions. The fractions finally obtained are termed A-E.

Fraction A.—The sirup (0.010 g.) had $[\alpha]_D^{26} - 22^\circ$ (c , 0.8 in H_2O) and R_f 0.98 in solvent A (found: OMe 47.9%; calc. for $\text{C}_8\text{H}_{16}\text{O}_6$: 48.4%) and was identified as 2,3,5-tri- O -methyl-L-arabinose by conversion into the lactone after oxidation with bromine water, $[\alpha]_D^{26} - 25^\circ$ (c , 0.7 in H_2O) and derived amide, m.p. and m.p. mixed with an authentic sample 135-137° C.

Fraction B.—The sirup (0.015 g.) had $[\alpha]_D^{25} + 20^\circ$ (c , 0.90 in H_2O) and R_f 0.94 in solvent A (found: OMe, 48.2%; calc. for $\text{C}_8\text{H}_{16}\text{O}_6$: 48.4%) and was identified as 2,3,4-tri- O -methyl-D-xylose, m.p. and mixed m.p. 90-92° C., $[\alpha]_D^{25} + 60^\circ \rightarrow +20^\circ$ (equil.) (c , 0.50 in H_2O).

Fraction C.—The sirup (2.09 g.) had $[\alpha]_D^{25} + 24^\circ$ (c , 1.40 in H_2O) and R_f 0.74 in solvent A (found: OMe, 34.4%; calc. for $\text{C}_7\text{H}_{14}\text{O}_6$: 34.4%), m.p. and mixed m.p. with 2,3-di- O -methyl-D-xylose 79-80° C., $[\alpha]_D^{25} + 60^\circ \rightarrow +23^\circ$ (equil.) (c , 1.10 in H_2O).

Fraction D.—The sirup (0.040 g.) had $[\alpha]_D^{25} + 72^\circ$ (c , 1.10 in H_2O) and R_f 0.87 (found: OMe, 42.2%; calc. for $C_9H_{18}O_6$: 41.9%); it solidified and was recrystallized from ether to give needles (0.030 g.), m.p. 137–139° C. In solvent *B* this substance had an R_f value different from that of 2,3,6- or 2,4,6-tri-*O*-methyl-D-glucoses. A small sample, on reduction with potassium borohydride and oxidation with sodium metaperiodate (10), gave a compound having an R_f value of 0.80 chromatographically identical with di-*O*-methyl-threose and another unknown material producing a color with chromic oxide and diphenylcarbazide and having an R_f value of 0.70. Fraction *D* remained unidentified since the melting point of this material is much higher than any recorded melting point of any tri-*O*-methyl derivatives of glucose, mannose, or galactose.

Fraction E.—This proved to be a mixture. The sirup (0.030 g.) had $[\alpha]_D^{26} + 21^\circ$ (c , 1.20 in H_2O) and R_f 0.50 in solvent *A* (found: OMe, 18.6%; calc. for $C_6H_{12}O_5$: 18.5%). A small sample of fraction *E* after methylation with silver oxide and methyl iodide gave only one substance, chromatographically identical with 2,3,4-tri-*O*-methyl-D-xylose. Another sample was examined by paper electrophoresis in a borate buffer of pH 10 and by applying a potential difference of approximately 450 v. between the ends of the paper for 10 hours. Spots corresponding to 3-*O*-methyl-D-xylose and 2-*O*-methyl-D-xylose were noted.

Reduction with Potassium Borohydride of the Acidic Fraction from the Methylated Xylan

The acidic fraction (0.230 g.), which was a mixture, was refluxed with methanolic hydrogen chloride (*N*) for 8 hours. After neutralization with silver carbonate the solution was taken to dryness and the resulting sirup (0.220 g.) was dissolved in water (2 ml.) and added slowly to a solution of potassium borohydride (0.1 g.) in water (2 ml.). After 1 hour the excess borohydride was destroyed by the addition of dilute acetic acid and the reduced oligosaccharides were collected (0.190 g.). The sirup was heated with sulphuric acid (*N*) at 100° C. for 9 hours and the hydrolyzate separated into four components (*A'*, *B'*, *C'*, and *D'*) by chromatography on Whatman 3 MM paper in solvent *A*.

Fraction A'.—The sirup (0.030 g.) had $[\alpha]_D^{25} + 70^\circ$ (c , 0.45 in H_2O) and R_f 0.86 in solvent *A* (found: OMe, 40.9%; calc. for $C_9H_{18}O_6$: 41.9%). Methylation of a portion of fraction *A'* and hydrolysis of the resulting methyl glycoside gave a compound chromatographically identical with 2,3,4,6-tetra-*O*-methyl-D-glucose. The remainder of fraction *A'* was reduced with potassium borohydride and oxidized with sodium metaperiodate (10). Examination of the product on a paper chromatogram revealed two substances, one chromatographically identical with 2,3,4-tri-*O*-methyl-D-xylose and another identical with di-*O*-methyl-threose, indicating that the original material was composed of a mixture of 2,3,6- and 2,3,4-tri-*O*-methyl-glucoses.

Fraction B'.—The sugar (0.030 g.) had $[\alpha]_D^{22} + 22^\circ$ (c , 0.86 in H_2O) and R_f 0.74 in solvent *A* (found: OMe, 34.2%; calc. for $C_7H_{14}O_5$: 34.4%) and was identified as 3,4-di-*O*-methyl-D-xylose by conversion into 3,4-di-*O*-methyl-D-xylonolactone, m.p. and mixed m.p. 62–65° C. and $[\alpha]_D^{25} - 50^\circ \rightarrow -22^\circ$ (equil.) (c , 0.42 in H_2O).

Fraction C'.—The sirup (0.020 g.) had $[\alpha]_D^{22} + 30^\circ$ (c , 0.80 in H_2O) and R_f 0.50 in solvent *A* (found: OMe, 18.2%; Calc. for $C_6H_{12}O_5$: 18.9%) and was found by paper electrophoresis to be a mixture of 2- and 3-mono-*O*-methyl-D-xyloses.

Fraction D'.—This fraction (0.040 g.) had R_f 0.00 to 0.30 in solvent *A* and was a mixture of unmethylated xylose and unreduced methylated uronic acids (paper chromatography). The paucity of acidic material made identifications difficult.

Quantitative Estimation of the Sugars Produced on Hydrolysis of the Methylated Xylan (Fraction 5)

A sample of the methylated xylan (0.170 g.) was hydrolyzed by heating it with aqueous formic acid (50%) followed by sulphuric acid (*N*). After neutralization with barium carbonate, the hydrolyzate was separated on extractive-free Whatman 3 MM paper in solvent *A*. The appropriate sections of the paper were extracted with methanol, the solution was filtered and taken to dryness. The proportions found were: R_f 0.94 (tri-*O*-methyl-pentose), 1; R_f 0.74 (di-*O*-methyl-pentose), 100; R_f 0.50 (mono-*O*-methyl-pentose), 2; R_f 0.00 to 0.30 (uronic acids), 40 (all by weight).

Hydrolysis of Fraction 8A: the Glucomannan

A sample of fraction 8A (0.078 g.), termed "glucomannan", was hydrolyzed by dissolving the polysaccharide in sulphuric acid (72%) at 20° C. After 12 hours water was added and the solution (*N* sulphuric acid) heated at 100° C. for 24 hours. The sulphuric acid was removed as barium sulphate and the residue separated on a cellulose column with *n*-butanol half saturated with water as the eluant. Four fractions were obtained. Fraction 1 (0.0015 g.) had $[\alpha]_D^{26} + 20^\circ$ (*c*, 1.12 in H₂O), its rate of movement relative to galactose (R_{gal}) was 1.9 in solvent *C*, and the osazone derivative had m.p. and m.p. mixed with the osazone of D-xylose 159–162° C. Fraction 2 (0.0272 g.) had $[\alpha]_D^{26} + 13^\circ$ (*c*, 1.24 in H₂O), R_{gal} 1.14 in solvent *C*, and the phenylhydrazone derivative had m.p. and mixed m.p. with the phenylhydrazone of D-mannose 199–202° C. Fraction 3 (0.0137 g.) had $[\alpha]_D^{26} + 54^\circ$ (*c*, 0.62 in H₂O), R_{gal} in solvent *C*, and the osazone derivative had m.p. alone and when mixed with the osazone of D-glucose 210–214° C. Fraction 4 (0.0016 g.), obtained by elution of the cellulose column with water, consisted of barium salts of acidic materials.

Methylation of the "Glucomannan"

The polysaccharide (1.6 g.) was methylated seven times with sodium hydroxide and methyl sulphate. The methylated polysaccharide soluble in chloroform–light petroleum (b.p. 60–80° C.) (1:4) was isolated (1.16 g.) and had $[\alpha]_D^{24} - 9.5^\circ$ (*c*, 1.04 in CHCl₃) (found: OMe, 43.8%).

Hydrolysis of the Methylated Glucomannan and Separation of the Sugars

The methylated material (0.970 g.) was heated at 100° C. in aqueous formic acid (50%) for 6 hours. The solvent was evaporated and the hydrolysis was continued for 24 hours at 100° C. with sulphuric acid (*N*). The sulphuric acid was removed as barium sulphate and the residue separated into four fractions by paper chromatography on sheets of extractive-free Whatman 3 MM paper in solvent *A*.

Fraction A.—The sirup (0.020 g.) had $[\alpha]_D^{26} + 2.4^\circ$ (*c*, 0.75 in H₂O), R_f 1.00 in solvent *A* (found: OMe, 51.9%; calc. for C₁₀H₂₀O₆: 52.5%), and was identified as 2,3,4,6-tetra-*O*-methyl-D-mannose by conversion of part of the sirup (0.018 g.) into the aniline derivative (0.0102 g.), m.p. 144–146° C. (identical when mixed with an authentic sample).

Fraction B.—The sirup (0.510 g.) had $[\alpha]_D^{26} + 10^\circ$ (*c*, 2.0 in H₂O) and R_f 0.80 in solvent *A* (found: OMe, 41.3%; Calc. for C₉H₁₈O₅: 41.9% and for C₇H₁₄O₅: 34.8%). Oxidation of a small sample with sodium metaperiodate revealed components chromatographically identical with 2,3,5-tri-*O*-methyl-arabinose and 2,3,6-tri-*O*-methyl-glucose. Reduction of another sample with potassium borohydride followed by oxidation with sodium metaperiodate revealed components chromatographically identical with 2,3,5-tri-*O*-methyl-arabinose,

di-*O*-methyl-erythrose, and di-*O*-methyl-threose. A portion of the sirup (0.184 g.) was oxidized with bromine water for 32 hours, the solution was aerated to remove the excess of bromine and neutralized with silver carbonate. The solution was filtered, saturated with hydrogen sulphide, and the water removed by distillation under diminished pressure. The residue was extracted with ether; removal of the ether left a sirup which was separated into three fractions B_1 , B_2 , and B_3 by paper chromatography, using extractive-free Whatman 3MM paper in solvent B ; each fraction was purified further by distillation under diminished pressure in a "cold finger" apparatus.

Fraction B_1 .—The sirup (0.0326 g.) had $[\alpha]_D^{26} + 56^\circ \rightarrow 32^\circ$ (equil.) (c , 1.50 in H_2O), R_f 0.82 in solvent B , and was identified as the furanolactone of 2,3,6-tri-*O*-methyl-D-gluconic acid by conversion to the phenylhydrazine derivative, m.p. and mixed m.p. 143–145° C.

Fraction B_2 .—The sirup (0.0756 g.) had $[\alpha]_D^{26} + 68^\circ$ (c , 0.52 in H_2O) and R_f 0.68 in solvent B , crystallized and was recrystallized from benzene–light petroleum (b.p. 60–80° C.) to give needles (0.052 g.) having m.p. and mixed m.p. (with the lactone of 2,3,6-tri-*O*-methyl-D-mannonic acid) 83–85° C. and $[\alpha]_D^{26} + 67^\circ \rightarrow +66^\circ$ (in 72 hours) (c , 0.68 in H_2O). In the mother liquor from the above crystallization the presence of 3,4,6-tri-*O*-methyl-mannonolactone and 2,3-di-*O*-methyl-xylonolactone was indicated chromatographically.

Fraction B_3 .—The sirup (0.0186 g.) had $[\alpha]_D^{26} + 60^\circ \rightarrow +40^\circ$ (equil.) (c , 0.85 in H_2O) and R_f 0.53 in solvent B . The phenylhydrazine derivative was prepared in very low yield and had m.p. 153–155° C. This substance gave an X-ray powder photograph different from that given by the phenylhydrazine derivative of 2,3,6-tri-*O*-methyl-D-gluconolactone.

Fraction C.—The sirup (0.0124 g.) had $[\alpha]_D^{26} + 60^\circ$ (c , 0.25 in H_2O) and R_f 0.55 in solvent A (found: OMe, 29.4%; calc. for $C_8H_{16}O_6$: 29.8%). On oxidation of a sample with sodium metaperiodate and chromatographic analysis, two components were noted, having R_f values 0.37 and 0.80. The component having R_f 0.37 is reported to be (10) methoxymalondialdehyde and is formed by oxidation of a 2,6-di-*O*-methyl-hexose. Demethylation of a small sample with hydrobromic acid (48%) and chromatographic analysis indicated mainly glucose with also smaller amounts of mannose.

Fraction D.—This fraction (0.0127 g.) consisted of mono-*O*-methyl-hexoses and methylated uronic acids (paper chromatography).

The Enzymic Hydrolysis of Hemicelluloses

A commercial preparation of a hemicellulose supplied by the Rohm and Haas Co. of Philadelphia was used. The powder (1 g.) was added to water (100 ml.) and the undissolved residue separated at the centrifuge. The solution was dialyzed against running water for 24 hours and again centrifuged; no reducing sugars were found in this solution (paper chromatography). This product will be called the "purified enzymes".

A solution of the purified enzymes was heated with sodium hydroxide (50 ml., 4 *N*) at 90° C. for 5 hours. The solution was cooled in ice, neutralized with hydrochloric acid, dialyzed against running water for 72 hours, and the water was distilled under diminished pressure. On hydrolysis with sulphuric acid (2 *N*) at 100° C. for 12 hours xylose, galactose, and mannose were indicated (paper chromatography).

Samples of the purified enzymes were heated at 37° C. and 45° C.; different solutions were prepared having pH values 5, 6, and 7. Toluene was added to the solutions and

the samples heated for 28 days. Aliquots were analyzed by paper chromatography and by the iodine consumed on reaction with hypoiodite. In all cases the presence of xylose, galactose, and mannose was indicated. Iodine numbers were nearly equal at the different pH values.

Substrate samples of the disaccharides glucuronosido-xylose, glucuronosido-galactose, and 4-O-methyl-glucuronosido-xylose were added to solutions having pH values of 2, 4, and 6. The appropriate amount of enzymes was added and the solutions heated at 45° C. for 72 hours; solutions containing approximately 10 μ g. of purified enzymes per gram of substrate were used. In all cases the disaccharides were hydrolyzed to the component sugars after the first hour (paper chromatography).

Less than 1% of untreated and milled aspen wood, but nearly 20% of the extractive-free and macerated wood, was hydrolyzed by a purified solution of the enzymes. The sugars produced and indicated chromatographically were the hexoses glucose, galactose, and mannose, the pentoses arabinose and xylose, and uronic acids. Nearly 5% of aspen α -cellulose was hydrolyzed; the sugars produced were mannose, glucose, galactose, xylose, and uronic acids. Hemicellulose fractions 1, 2, and 3 (cf. Table I) were resistant to attack by a purified solution of the enzymes; fraction 4 was hydrolyzed completely; and fraction 5 to an extent of 80%.

Enzymic Hydrolysis of Fraction 5

A sample of fraction 5 (10 g.) was suspended in water (2 liters) and the appropriate amount of a solution of the purified enzymes added. Toluene was added and the solution kept at 45° C. for 7 days. Ethanol (200 ml.) was then introduced and the solution placed in a number of dialysis containers. These were immersed in distilled water and the solution was agitated gently; the water was renewed every day for 7 days; a total of 20 liters of solution was collected. The solution inside the cellophane containers was again treated with a purified solution of the enzymes and the cycle repeated four times as before. The residue resistant to hydrolysis by the enzymes (1.5 g.) on hydrolysis with sulphuric acid (*N*) showed the presence of xylose, and traces of arabinose, rhamnose, mannose, glucose, and acidic materials.

The solutions which passed through the membranes were concentrated to a sirup (8.0 g.) which was separated into two fractions by chromatography on a column of Amberlite IR-4B (acetate form) resin: a neutral fraction (6.2 g.) and an acidic fraction (1.7 g.) were obtained. A second larger sample of fraction 5 (80 g.) was hydrolyzed by the enzymes and the reducing sugars isolated as described above.

Identification of the Constituent Sugars of the Neutral Fraction Produced on Enzymic Hydrolysis of Fraction 5

The sirup (6.2 g.) solidified and was recrystallized from aqueous ethanol to give D-xylose (4.7 g.) having m.p. and mixed m.p. 147° C. and $[\alpha]_D^{25} + 19^\circ$ (equil.) (*c*, 1.10 in H₂O). The mother liquor was separated into seven fractions by chromatography on cellulose using first *n*-butanol half saturated with water followed by water as the eluant.

Fraction 1 (0.100 g.) had $[\alpha]_D^{25} + 9^\circ$ (equil.) (*c*, 0.94 in H₂O) and after recrystallization from ethanol had m.p. and mixed m.p. with L-rhamnose hydrate 95° C. Fraction 2 (0.350 g.) had $[\alpha]_D^{25} + 20^\circ$ (equil.) (*c*, 1.19 in H₂O) and after recrystallization from methanol had m.p. and mixed m.p. with D-xylose 147° C. Fraction 3 (0.120 g.) had $[\alpha]_D^{25} + 102^\circ$ (equil.) (*c*, 0.82 in H₂O) and after recrystallization from methanol had m.p. and mixed m.p. with L-arabinose 156–158° C. Fraction 4 (0.093 g.) had $[\alpha]_D^{25} + 13^\circ$ (*c*, 0.22 in H₂O)

and the phenylhydrazone derivative had m.p. and mixed m.p. with the phenylhydrazone derivative of D-mannose 199–201° C. Fraction 5 (0.043 g.) had $[\alpha]_D^{22} + 54^\circ$ (c, 0.10 in H₂O) and the osazone derivative had m.p. and mixed m.p. with the osazone of D-glucose 210–214° C. Fraction 6 (0.050 g.) had $[\alpha]_D^{22} + 26^\circ$ (c, 0.20 in H₂O) and the osazone derivative had m.p. and mixed m.p. with the osazone of xylobiose 210–212° C. Fraction 7 (0.320 g.) was a complex mixture of oligosaccharides. On hydrolysis with sulphuric acid (N) at 100° C. for 7 hours the presence of xylose was indicated (paper chromatography) as the only monosaccharide.

Identification of the Constituent Sugars of the Acidic Fraction Produced on Enzymic Hydrolysis of Fraction 5

The sirup (1.7 g.) was separated into four fractions by chromatography on cellulose using ethyl acetate – acetic acid – water (9:2:1), changing to ethyl acetate – acetic acid – water (9:2:2), to aqueous acetic acid, and finally to water as the eluants. Fraction 1 (0.150 g.) had $[\alpha]_D^{24} + 25^\circ$ (c, 0.60 in H₂O) and R_f 0.66 in solvents A, B, D, and E (found: OMe, 20.2%; E.W., 497), had m.p. 152–154° C., was unstable, and showed an ultra-violet absorption with a maximum at 254 mμ (optical density). On hydrolysis with sulphuric acid (N) at 100° C. for 2 hours fraction 1 yielded 4-O-methyl-glucuronic acid and an unknown compound having R_f 0.98. Possibly the latter was an aromatic aglycone. Fraction 2 (0.450 g.) had $[\alpha]_D^{24} + 75^\circ$ (c, 0.98 in H₂O); the derived methyl-α-4-O-methyl-D-glucuronamide had m.p. 236° C. and $[\alpha]_D^{20} + 150^\circ$ (c, 1.02 in H₂O); the derived methyl-β-4-O-methyl-D-glucuronamide had m.p. 236° C. and $[\alpha]_D^{20} - 50^\circ$ (c, 1.04 in H₂O). Fraction 3 (0.108 g.) had $[\alpha]_D^{24} + 18^\circ$ (c, 0.94 in H₂O); on reduction with potassium borohydride and hydrolysis D-glucose was formed having m.p. 145–148° C. and $[\alpha]_D^{25} + 53^\circ$ (equil.) (c, 0.43 in H₂O). The presence of a small amount of galactose was also indicated. Fraction 4 (0.500 g.) was composed of a large number of oligosaccharides; on hydrolysis with sulphuric acid (2 N) at 100° C. for 18 hours the presence of xylose, glucose, rhamnose, and acid residues was indicated.

Properties of the Polysaccharide Resistant to Enzymic Degradation: The Residual "Xylan"

The material had $[\alpha]_D^{24} - 76^\circ$ (c, 1.02 in H₂O), the uronic anhydride content was 4.1% (6), and the lignin 2.9% (13, p. 369). Quantitative estimation, by the method of Hirst and Jones (4), of the sugars produced on hydrolysis with sulphuric acid (N) at 100° C. for 12 hours, indicated the presence of the following (calculated as proportions of sugar residues in the original xylan): xylose (74 parts), arabinose (6 parts), hexoses (2 parts), and rhamnose (less than 1 part).

Methylation of the Residual Xylan and Identification of the Component Sugars

A sample of this material (11 g.) was methylated nine times with sodium hydroxide and methyl sulphate; the methylated polysaccharide was extracted as previously described (8.1 g.) and had $[\alpha]_D^{23} - 66^\circ$ (c, 1.30 in CHCl₃) (found: OMe, 37.5%). The methylated material was hydrolyzed with aqueous formic acid (50%) followed by sulphuric acid (N) and the hydrolyzate was separated on columns of cellulose powder and on paper into six fractions (A–F). Fraction A (0.010 g.) had $[\alpha]_D^{25} + 1.3^\circ$ (c, 0.34 in H₂O), R_f 1.00 in solvent A, and the aniline derivative had m.p. and mixed m.p. (with the aniline derivative of 2,3,4,6-tetra-O-methyl-D-mannose) 147–148° C. (found: OMe, 40.3%; calc. for C₁₆H₂₆O₅N: 39.8%). Fraction B (0.020 g.) had $[\alpha]_D^{25} - 20^\circ$ (c, 0.76 in H₂O), R_f 0.98 in solvent A (found: OMe, 47.9%; calc. for C₈H₁₆O₅: 48.4%), and was identified

as 2,3,5-tri-*O*-methyl-L-arabinose by conversion to the amide derivative, having m.p. and mixed m.p. 135–137° C. Fraction *C* (0.020 g.) had $[\alpha]_D^{25} + 21^\circ$ (*c*, 1.0 in H₂O), *R*_f 0.94 in solvent *A* (found: OMe, 48.0%; calc. for C₈H₁₆O₅: 48.4%), and was identified as 2,3,4-tri-*O*-methyl-D-xylose, m.p. and mixed m.p. 90–92° C. Fraction *D* (5.2 g.) had $[\alpha]_D^{25} + 23^\circ$ (*c*, 2.0 in H₂O), *R*_f 0.74 in solvent *A* (found: OMe, 34.1%; calc. for C₇H₁₄O₅: 34.4%), and was identified as 2,3-di-*O*-methyl-D-xylose, m.p. and mixed m.p. 79–80° C. Fraction *E* (0.020 g.) had $[\alpha]_D^{25} + 122^\circ$ (*c*, 0.80 in H₂O), *R*_f 0.80 in solvent *A*. The lactone derivative had $[\alpha]_D^{22} + 140^\circ \rightarrow +40^\circ$ (equil.) (*c*, 0.42 in H₂O) and was believed to be a derivative of 2,3,4-tri-*O*-methyl-L-arabinose. Fraction *F* (0.070 g.) had $[\alpha]_D^{25} + 20^\circ$ (*c*, 0.62 in H₂O), *R*_f 0.50 in solvent *A* (found: OMe, 18.5%; calc. for C₆H₁₂O₅: 18.9%), which paper electrophoresis indicated to be a mixture of 2- and 3-mono-*O*-methyl-D-xyloses.

The acidic fraction (0.300 g.), which behaved as three components, was reduced with potassium borohydride and treated in a way analogous to that described for the original xylan. A mixture of 2,3,4- and 2,3,6-tri-*O*-methyl-D-glucoses and of 2- and 3-mono-*O*-methyl-D-xyloses was indicated to be present and 3,4-di-*O*-methyl-D-xylose was identified.

After quantitative hydrolysis of the methylated residual polysaccharide resistant to enzymic degradation, the following proportions were found: *R*_f 0.94 (tri-*O*-methyl-pentose) 1 part; *R*_f 0.74 (di-*O*-methyl-pentose) 80 parts; *R*_f 0.50 (mono-*O*-methyl-pentose) 1 part; *R*_f 0.00 to 0.30 (uronic acids) 10 parts. Details are given of the analysis of fraction 5 under the section entitled "Quantitative Estimation of the Sugars Produced on Hydrolysis of the Methylated Xylan (Fraction 5)". It will be observed that enzymic degradation has altered but slightly the relative proportions of sugars.

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POLAROGRAPHIC BEHAVIOR OF THE VIOLOGEN INDICATORS¹

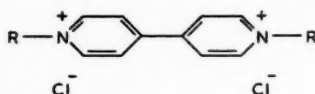
R. M. ELOFSON AND R. L. EDSBERG²

ABSTRACT

The polarographic behavior of 1,1'-dimethyl- and 1,1'-dibenzyl-4,4'-bipyridinium dichloride has been investigated over the pH range of 1 to 13. Reversible reduction waves are obtained for the first single-electron step for both compounds. The second step is electrochemically irreversible but evidence is presented to indicate that the second step is fleetingly reversible at the dropping mercury electrode for methyl viologen but not benzyl viologen. Minor waves due to adsorption of the reduced viologen on the surface of the mercury have been observed.

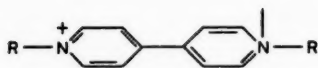
INTRODUCTION

The viologen indicators (3) (e.g. 1,1'-dimethyl- and 1,1'-dibenzyl-4,4'-bipyridinium chloride I and II) undergo reversible one-electron reduction to produce very intensely colored violet solutions. These colored substances have been definitely shown to be free radicals and may be represented by structures such as III or IV (2, 8). Two-electron reduction results in structures which can be represented by V, a biradical, or VI, in which the electrons have become paired (6). Weitz (10) concluded from the behavior, such

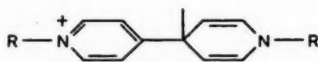


I R = METHYL

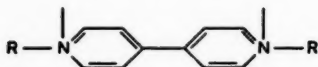
II R = BENZYL



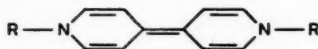
III



IV



V



VI

as oxidizability in air, of these latter compounds that he was working with biradicals and that, in fact, he had biammonium radicals, which would be the only structures in which pairing of the electrons would not be likely to occur. However, Mueller (6) by means of magnetic measurements on the benzyl derivative has shown that the product of a single-electron reduction is paramagnetic while that of a two-electron reduction is diamagnetic, which indicates that pairing of electrons has occurred as in VI. Michaelis and Hill (4), during their studies on semiquinones, investigated the first step of the reduction by potentiometric titration. They could only make the titrations at pH greater

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than 9 because at lower pH the potentials were so negative as to exceed the overvoltage of hydrogen on platinum. They could not, of course, attempt a study of the second step of the reduction. Mueller (5) investigated the polarographic behavior of methyl viologen and confirmed the expectation that for the first step of the reduction the potentials were independent of pH over the entire pH range.

In the present investigation it has been confirmed that the first step of the reductions for both methyl and benzyl viologen is independent of pH and agrees closely with the potentiometric data. Further, it has been found that the second step of the reduction is also independent of pH. The nature of this second wave and certain other waves has been examined in detail.

EXPERIMENTAL

The polarograph used for the data presented in Tables I and II was built in the laboratories of the General Aniline and Film Corporation, and has been reported previously (1). For this work the dropping mercury electrode had the following characteristics:

$$t = 4.6 \text{ seconds, } m = 1.56 \text{ mg./second, and } h = 92 \text{ cm.}$$

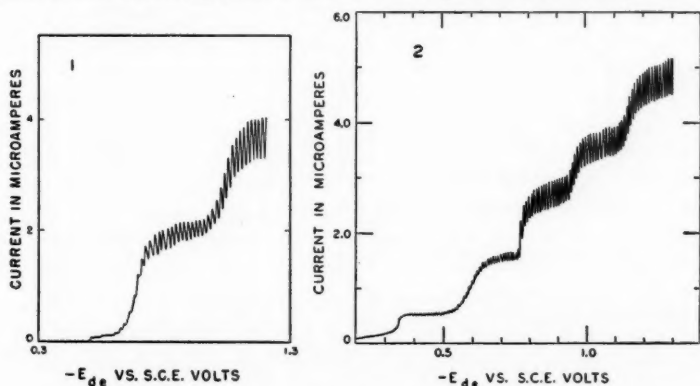
Further studies—the controlled potential electrolyses, the effect of temperature, and the polarogram of Fig. 2—were carried out with a Leeds and Northrup Electrochemograph Model E at the Research Council of Alberta. The buffered solutions were prepared according to Clark and Lubs.

The determinations of half-wave potential were made with increasing and decreasing potentials to minimize the instrumental lag.

Investigation of the effect of height of the mercury column showed that all waves except the adsorption waves mentioned in the text were diffusion controlled.

RESULTS

Fig. 1 shows a polarogram prepared on methyl viologen at pH 9. The first reduction step occurs at $E_{\frac{1}{2}} = -0.680$ o.v. vs. S.C.E., or -0.434 v. vs. N.H.E., which is in satisfactory agreement with the potentiometric value of -0.446 v. (4). In Fig. 3 confirmation of the fact that the first step corresponds to a single-electron reduction is shown by the plot of $\log[i/(i_d - i)]$ vs. E_{de} , which produces a straight line with an inverse slope of 0.061 v. in good agreement with the theoretical value of 0.059 v. for a one-electron reduction. Because the second step of the reduction has a height equal to that of the first, the conclusion is that it corresponds to the second step of the reduction, V or VI.



FIGS. 1 AND 2.

Table I shows the results for methyl viologen over the entire pH range. The first step of the reduction occurs at a constant potential of $0.678 \pm .002$ v. The second step occurs at a potential of -1.038 v. in the pH range 5–13. Below this range the second wave occurs at a potential that decreases with pH, and it is irregular in shape. Because of the discharge of hydrogen, it is not possible to study the wave in this range.

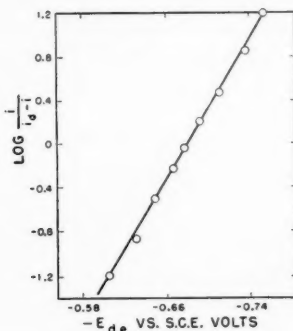


FIG. 3.

Fig. 2 shows a polarogram made on benzyl viologen at a pH of 9. The first step at -0.597 v. vs. S.C.E. (0.331 v. vs. N.H.E.) is in excellent agreement with that found by potentiometric titration of -0.359 v. vs. N.H.E. (4). The second step in the reduction occurs at -0.78 v. vs. S.C.E. but from its shape clearly corresponds to an irreversible process. In addition, two more steps which may correspond to the third and fourth electron steps are observed. However, these latter waves change in height and position with pH. Table II shows that the half-wave potentials of the first two waves are constant over

TABLE I
POLAROGRAPHIC HALF-WAVE POTENTIALS OF METHYL VIOLOGEN VS. S.C.E.
Temp. 25°C ., concn. $4.5 \times 10^{-4} M$

pH		$E_{1/2}$ first wave, volts	$E_{1/2}$ second wave, volts
1.15	0.1 N HCl	-0.678	-0.890
1.55	0.1 N H ₂ SO ₄	-0.676	-0.884
2.1		-0.677	-0.917
3.1		-0.679	-0.934
4.0		-0.677	-0.980
5.0		-0.678	-1.036
5.6		-0.680	-1.038
8.0		-0.678	-1.033
9.0		-0.680	-1.040
11.5	0.1 N NaOH	-0.678	-1.039
		-0.677	-1.043
Av. -0.678		Av. (pH 5-13)	-1.038

the entire pH range and equal -0.592 v. and -0.792 v. vs. S.C.E. respectively. The constancy of the potential of the second wave with pH is not as good as for the methyl viologen but this is to be expected of such sharply irreversible waves.

TABLE II
POLAROGRAPHIC HALF-WAVE POTENTIALS OF BENZYL VIOLOGEN VS. S.C.E.
Temp. 25° C., concn. 4.5×10^{-4} M

pH		$E_{1/2}$ first wave, volts	$E_{1/2}$ second wave, volts
1.15	0.1 <i>N</i> HCl	-0.594	-0.785
2.0		-0.591	-0.793
5.6		-0.589	-0.804
7.0		-0.594	-0.776
9.0		-0.597	-0.787
10.0	0.1 <i>N</i> NaOH	-0.591	-0.767
		-0.589	-0.762
		Av. -0.592	-0.782

In addition to these major waves, a small wave occurs at -0.35 v. vs. S.C.E. with benzyl viologen. This wave has been proved to be an adsorption wave by the fact that it does not increase in height with increase in concentration beyond a certain limit and by the fact that its height varies directly with the height of the mercury in the reservoir (2). Only a trace of such a wave occurs in the polarograms on methyl viologen. Since the wave is at a more positive potential than the main wave, it corresponds to adsorption of either the singly or the doubly reduced material at the electrode (2). These waves have been taken into consideration in computing the values of E_0 from Tables I and II.

For methyl viologen the second step of the reduction is the final step at the dropping mercury electrode, whereas with benzyl viologen subsequent steps are observed. While the nature of these has not been investigated in detail, they are dependent on pH and may correspond to further reduction involving hydrogen ions. This may indicate that with methyl viologen the biammonium radical V is temporarily stabilized towards further reduction whereas with benzyl viologen it is not.

The reversibility of the first step of the reduction has been demonstrated polarographically in this investigation by chemical reduction with reducing agents such as sodium hydrosulphite, and zinc and ethyl alcohol. Polarograms on the reduced solutions produced anodic or anodic-cathodic waves at potentials corresponding to the first wave of the reduction. Similar results were obtained by controlled potential electrolyses on both compounds at potentials on the plateaus between the first and second waves.

Quite different results were obtained when attempts were made to show the presence of anodic waves corresponding to the second stage of reduction. Chemicals which are known to produce the products of two-electron reductions (10), such as sodium amalgam, and zinc and sodium hydroxide, were used to reduce the solutions but no anodic waves were produced. Controlled potential electrolyses at the second plateaus likewise produced no anodic waves. The passage of oxygen through these cells, however, resulted in the return of the original viologen; therefore the conclusion is that the second step of the reduction is not reversibly active at the electrode although it can be reoxidized by the air. The fact that material corresponding to the second step of the reduction but not to the first has been isolated and maintained in the solid state in air supports this view. Apparently therefore the product of two-electron reduction in solution corresponds to formula VI, which is supported by the magnetic measurements of Mueller (6).

However, the polarograms indicate that, whereas for benzyl viologen the second

step of the reduction is clearly irreversible, the second step of the reduction of methyl viologen may be fleetingly reversible. The evidence for this is:

(1) With the methyl viologen the second wave is symmetrical and corresponds to a reversible one-electron reduction; the second benzyl viologen wave does not.

(2) The E_1 of the methyl viologen wave is nearly independent of temperature, whereas the wave for benzyl viologen has a temperature dependence of -3 mv./°C. (2).

Mueller (7) and others (9) have produced biradicals in such systems by preventing the overlapping and pairing of the π -orbitals by substitution in the ortho-positions to prevent planarity. If such compounds can be prepared, polarographic waves corresponding to the second wave of methyl viologen may be obtained, but it should be possible in addition to obtain corresponding anodic waves.

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SYNTHESIS IN THE FIELD OF THE ERYTHRINA ALKALOIDS

PART I. THE SYNTHESIS OF HEXAHYDROAPOERYSTRINE¹

B. BELLEAU

ABSTRACT

The synthesis of the complete ring system of the aromatic class of *Erythrina* alkaloids is described. The basic sequence involves reaction of hexahydroindole (whose preparation was studied in some detail) with phenylacetyl chloride to give the ketoamide (VII) which suffered ring closure to the desired ring system (XI) when treated with polyphosphoric acid. Reduction of XI with lithium aluminum hydride gave the corresponding base (XIII). Evidence in support of structure XI is presented. Application of the same sequence with homoveratroyl chloride as starting material led ultimately to the spiroamine (XIV) which proved identical with a sample of natural origin. The stereochemistry of the spiroamines is discussed and the reaction mechanisms involved are critically examined. The new cyclization reaction was successfully applied to the system phenylacetamide-cyclohexanone in an effort to explore its scope.

In 1951, Prelog and co-workers (5) presented convincing evidence that the aromatic class of *Erythrina* alkaloids must be assigned the basic structure I although at that time the exact position of the ring D methoxyl was not established. Most members of this class of alkaloids differ from one another mainly in the nature of the substituents in ring A, and evidence on that point was adduced by the conversion of two important members (namely erysodine and erythraline) to a common base (II), erysotrine. A complete description of the evidence concerning their structure has been reviewed by Boekelheide (4) and more recently by Prelog (13) and it may be only necessary to mention that Prelog and his group (15) have confirmed their previous deductions and elucidated the conformation of erythraline by an X-ray investigation which also revealed the exact position of the ring D methoxyl. Moreover, the stereochemistry of the corresponding tetrahydro derivative (III) of erythraline could be inferred and in all probability possesses a *trans* arrangement about the perhydroindole moiety, a prediction in agreement with the probable course of hydrogenation of the rigid ring system of erythraline. By analogy, hydrogenation of apoerysotrine to hexahydroapoerysotrine (IV) should in all probability lead to a *trans* configuration. The latter base (IV) includes the complete and unarranged ring system of this class of *Erythrina* bases and appeared more susceptible to approach by synthesis than the native alkaloids. Moreover, it was hoped that such spiroamines as IV might be of pharmacological interest.

At the time the present investigation was initiated, Wiesner and his group (18) described an interesting approach directed at the synthesis of the intact ring system of this class of alkaloids. However, their efforts have not been fruitful as yet, but more significantly they were successful in synthesizing apoerysopine dimethyl ether which proved identical with a sample of natural origin (5). Apoerysopine being related to the natural alkaloids through a rearrangement, the task remained to elaborate synthetically the intact skeleton as present for instance in hexahydroapoerysotrine (IV).

An obvious approach to the desired ring system would involve ring closure of the quaternary Schiff base V to IV, a possibility patterned after Boekelheide's scheme (4)

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Contribution from the Department of Biochemistry, School of Medicine, Laval University, Quebec, Que. This work was first presented at the Eighth Summer Seminar on the Chemistry of Natural Products held at Grand Manan, N.B., Aug. 5-12, 1956. Preliminary communications have already been published (Refs. 2 and 3).

for the biogenesis of the various *Erythrina* bases. The close analogy of this presumption with the classical Pictet-Spengler ring closure (17) justified the preparation of quaternary salt V in order to test the possibility of cyclization to IV. Intermediate V was readily obtained as a hygroscopic solid from homoveratryl bromide and hexahydroindole, the preparation of which is described in detail later in this paper. However, all attempts at effecting ring closure to IV under a variety of conditions proved fruitless, unchanged starting material being recovered.* In order that these negative results be rationalized and serve as a basis for further discussion, it becomes necessary at this point to examine briefly some of the features of the classical Pictet-Spengler synthesis (P-SS) of tetrahydroisoquinolines (THI) (17). The most remarkable feature of the P-SS lies in its great sensitivity toward minor structural variations about either the carbonyl or the aromatic component. Thus, a brief survey of the literature suffices to see that as the number of substituents on the trigonal carbon of intermediate VI increases, the yield of THI tends to decrease markedly. It is possible to detect a clear-cut detrimental effect of a single alkyl group on the yield of THI and this may be illustrated by the unsuitability of simple aliphatic aldehydes in the P-SS under pseudophysiological conditions provided the aromatic component is activated by alkoxy groups only. Indeed, under such conditions only formaldehyde is known to lead to important yields of THI and it is necessary to effect condensation in hot concentrated hydrochloric acid if other aldehydes are used as intermediates. Moreover, even under the best experimental conditions, ketones lead only to low yields of cyclized products (8) and it becomes clear therefore that the success of the P-SS is largely dependent upon the number of alkyl groups present on the trigonal carbon of VI. It is of interest that in some instances it is possible to overcome the detrimental effect of alkyl groups by an appropriate increase in activation of the aromatic component. This is illustrated by the successful pseudo-physiological condensation of certain aralkylaldehydes with phenethylamines when the activating groups are hydroxyls. It is obvious therefore that a very delicate balance between the electrophilicity of the trigonal carbon of VI and the activation of the aromatic ring is a major characteristic of the P-SS, and small alterations of this balance by alkyl groups are principally ascribable to the inductive effect ($+I$) of the alkyl groups resulting in a discrete but critical decrease in electrophilicity of the trigonal carbon. These serious limitations to the P-SS contrast sharply with the generality of the Friedel-Crafts alkylation of aromatic nuclei with carbonyl compounds even though both reactions are mechanistically closely related. This marked difference in scope between the two reactions closely parallels the twofold difference in bond moment between the imine and carbonyl double bonds (7), and it can be seen that if the bond moment of the imine or immonium double bond could be increased to approach that of the carbonyl double bond, the scope of the P-SS would then parallel that of the Friedel-Crafts reaction. It was therefore of considerable interest to devise means by which the polarization of the immonium double bond of V would be increased, since it is obvious from the above line of reasoning that the quaternary Schiff base V did not stand a chance to undergo ring closure. One way of accomplishing this would be to introduce a carbonyl group adjacent to the nitrogen atom. It can be predicted that such an amide carbonyl group will increase the electrophilic character of the trigonal carbon in two ways: (a) through its strong $-I$ effect transmitted by the nitrogen to the reactive carbon and (b) through a resonance effect

*In a private communication, Professor Wiesner has informed the author that similar results were obtained in his laboratory.

leading to a hybrid between two extreme forms A and B, the latter being presumably incapable of existence in that form because of the two adjacent positive charges. In this manner, the polarization of the immonium double bond should be considerably increased



and may well approach the state of affairs obtained in the Friedel-Crafts alkylation with carbonyl compounds. The ketoamide (VII) appeared as the best choice* for our purposes since it seemed unlikely that the amide carbonyl group as such would be capable of alkylating either the aromatic ring or other points in the molecule.† This ketoamide (VII) was readily obtained from phenylacetyl chloride and hexahydroindole and heated to 100° for several hours in a 50:50 mixture of phosphorus pentoxide – phosphoric acid to give, in 60% yield, a single crystalline substance analyzing correctly for structure XI and which exhibited strong absorption in the infrared at 6.14 μ , in agreement with a six-membered substituted lactam. The compound proved inert toward acid or alkaline hydrolysis, thus fixing the potential carboxyl and amino groups in close steric proximity as required by a six-membered lactam but not by a higher-membered lactam. Such refractoriness of a six-membered lactam toward hydrolysis is not unique and has been observed before in the morphinane series (9). Vigorous oxidation of XI with nitric acid led to the isolation of 4-nitrophthalic acid, thus establishing conclusively that alkylation of the benzene ring had occurred in the anticipated manner. Finally, lithium aluminum hydride reduction of XI gave the corresponding base (XIII), which formed well-crystallized salts.

The success in bringing about cyclization of intermediate IX, which obviously arises from the ketoamide VII in the acid medium, adds considerable weight to the above generalizations and may open a new way to a variety of substituted tetrahydroisoquinolines hitherto inaccessible by the conventional Pictet-Spengler synthesis. Another point of interest in structure XI is the probable configuration about the perhydroindole moiety which is tentatively considered to be “*trans*” on the basis of arguments described below.

From these results, it became apparent that substituting homoveratroyl chloride for phenylacetyl chloride in the above sequence would offer no difficulty and would even facilitate ring closure by virtue of the activating methoxy groups on the benzene ring.‡ Thus, reacting homoveratroyl chloride with hexahydroindole afforded the ketoamide VIII in 93% yield which underwent smooth ring closure to XII in 73% yield when heated for a few hours in a phosphorus pentoxide – phosphoric acid mixture. Subsequent reduction with lithium aluminum hydride gave the corresponding base (XIV) whose dimorphic picrate had an infrared spectrum indistinguishable from that of a sample of hexahydroapoerysotrine picrate kindly supplied by Professor V. Prelog. Resolution of the synthetic base was successfully accomplished through the dibenzoyltartrate salt to give the levorotatory base, $[\alpha]_D^{24} = -43^\circ$ (reported (14): -39°), whose picrate had

*A preliminary account of this work has appeared elsewhere (2).

†Long after this work was first reported, a preliminary report was published by Mondon (11) on the ring closure of the isomeric amide obtainable from homoveratryl amine and 2-oxocyclohexane – acetic acid. It is of interest that Bishler-Napieralsky ring closure does not appear to take place as might have been anticipated with this isomeric amide.

‡A preliminary report covering this portion of the work has already appeared (3).

m.p. 205–207°, not depressed upon admixture with the sample of natural origin (itself melting at 205–206° (14)). Finally, the infrared spectra of the picrates were identical in every respect. Thus, the structural assignments deduced by Prelog from degradative evidence concerning the basic ring system of the aromatic *Erythrina* alkaloids are fully substantiated. From the fact that hexahydroapoerysotrine possesses in all probability a “*trans*” configuration (see above) and that ring closure of ketoamide (VIII) to lactam (XII) is stereospecific in that only one product was obtained (the presence of a second isomer could not be detected), the conclusion must be reached that there exists a mechanistic or conformational barrier to the formation of a “*cis*” isomer during the process of cyclization of the intermediate immonium ion (X). The recent findings of Barnes (1) may have a bearing on the mechanistic aspect of this reaction although conformational restrictions may also be of importance. However, an attempt at such a conformational interpretation clearly leads to the prediction of a “*cis*” configuration for the ring-closed

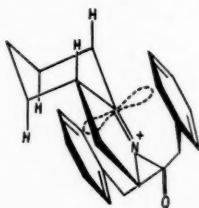


FIG. 1.

products as can be seen in Fig. 1. Molecular models of the transition state (Fig. 1) show a much smaller degree of hindrance to approach by the phenyl ring on the top of the plane (passing through the four atoms linked to the immonium double bond). Approach from under the plane is hindered by two axial hydrogens. Since a “*trans*” arrangement about the perhydroindole moiety is the most probable one as judged from the investigations of Prelog, it becomes clear that other factors must come into play and a detailed knowledge of the exact mechanism of cyclization would be necessary before this matter could be discussed further. A tentative explanation might be that the immonium ion (Fig. 1), is highly solvated by bulky polyphosphate anions on the top of the plane, thus forcing approach of the phenyl ring from under the plane.

It is of interest to note that, regardless of the configuration, the ready cyclization of X to XII provides so to speak a chemical confirmation of Boekelheide's biogenetic scheme in the sense that the amide carbonyl group serves as the essential activator of the immonium bond and acts as a substitute for enzymatic activation as in the plant.

The success in cyclizing amides of the type of VII raised the possibility of applying this new approach to the synthesis of tetrahydroisoquinoline derivatives that have remained hitherto inaccessible by the P-SS. As an example, an extreme case would involve condensation of a ketone with 2-phenethylamine, the latter being incapable of giving any tetrahydroisoquinolines even with formaldehyde as the carbonyl component. In fact, when equimolar amounts of phenylacetamide and cyclohexanone were heated to 100° for a few hours in excess polyphosphoric acid, there was obtained a 35% yield of a crystalline lactam, formulated as XV on the basis of empirical composition, ultraviolet spectrum (only benzenoid absorption), and refractoriness toward hydrolysis. It may seem therefore that application of this new method may deserve attention wherever the P-SS fails.

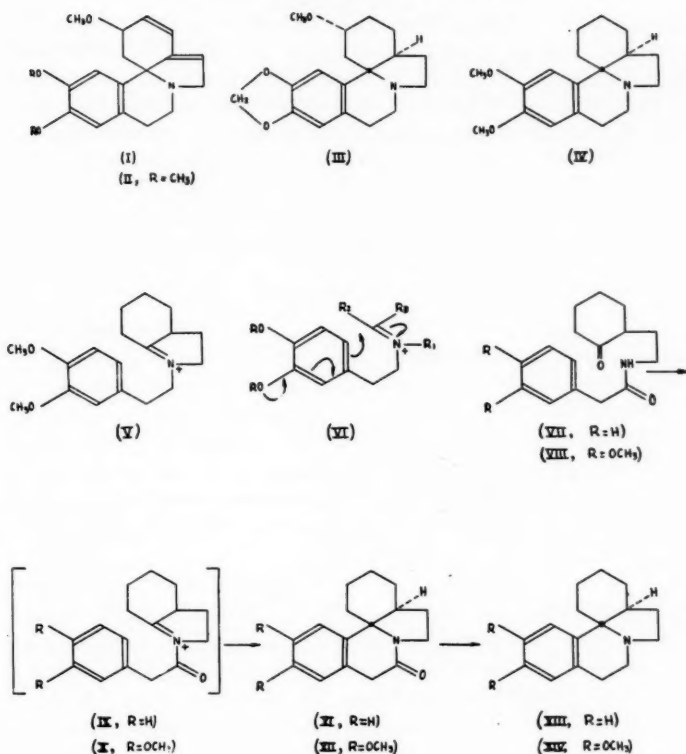


CHART I.

The Preparation of Hexahydroindole

The basic starting material hexahydroindole (XVII) was prepared by three different methods, the last one described being preferred for reasons of convenience. King and co-workers (10) were the first to obtain hexahydroindole, which they prepared by hydrogenation of 2-(2'-nitroethyl)cyclohexanone (XVI). The latter nitroketone was obtained in a reported yield of 30% (to be compared with a reported yield of 70% by Reichert and Posemann (16) from 2-dimethylaminocyclohexanone and nitromethane. In our hands, the best yields of pure nitroketone (XVI) never exceeded 15%, a result at variance with those of King *et al.* However, reduction of XVI over Raney nickel proceeded smoothly to give an 80% yield of hexahydroindole which proved resistant to further hydrogenation with that catalyst. In our earlier report (2), the base was arbitrarily assigned an enamine structure which must now be changed to the ketimine structure (XVII) on the basis of a recent infrared investigation by Witkop (20). Structure XVII for the base was confirmed by quantitative hydrogenation over Adams' catalyst in ethanol to *cis*-octahydroindole, whose picrate proved identical with octahydroindole picrate prepared according to Willstätter and Jacquet (19). All attempts to improve the yield of 2-nitroethylcyclohexanone were fruitless. It therefore became necessary to explore other methods of preparation of XVII. Condensation of 2-bromoethylphthalimide with 2-ethoxycarbonylcyclohexanone would be expected to yield XVIII, which on

hydrolysis should lead to XVII. These expectations were realized and the base XVII obtained in 35–40% over-all yield. Unfortunately, this method was not easily adaptable to large-scale preparations and a third but somewhat longer sequence was finally developed which offers the advantage of greater versatility. Thus, condensation of 2-chlorocyclohexanone (12) with ethyl cyanoacetate in the presence of sodium ethoxide in benzene

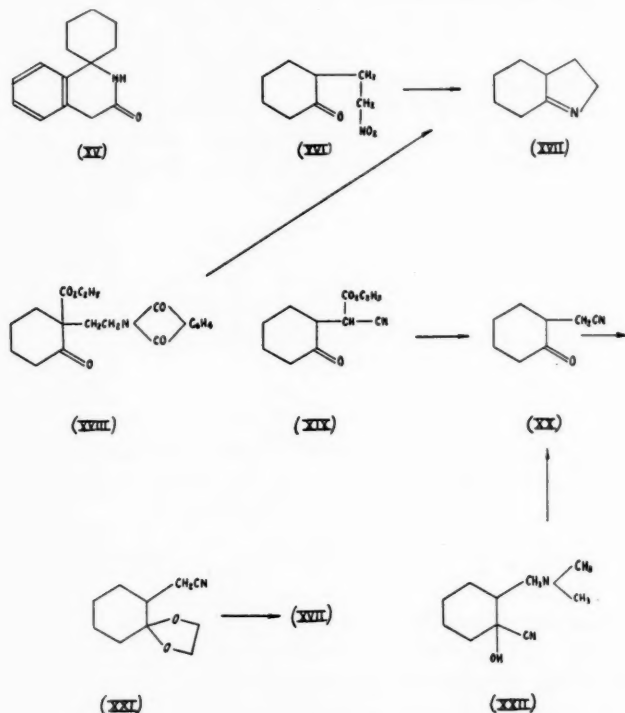


CHART II.

gave ethyl α -cyano-2-oxocyclohexane acetate (XIX) in 65–70% yield which was partially saponified and decarboxylated to 2-oxocyclohexane acetonitrile (XX) in 60% yield (based on the ester). The latter was ketalized to XXI in over 90% yield using ethylene glycol followed by lithium aluminum hydride reduction in tetrahydrofuran and mild acid hydrolysis, to yield hexahydroindole in 70% yield (based on XXI). The low pressure catalytic hydrogenation of XX or XXI using Raney nickel as the catalyst also afforded hexahydroindole (XVII) in lower yields.

Recently, Dornow and Fleischmann (6) reported on an alternative preparation of 2-cyanomethylcyclohexanone (XX) which considerably shortens the preceding sequence. They found that dimethylaminocyclohexanone cyanohydrin (XXII) can be converted in 80% yield to XX by simply heating to 150°. In this manner, hexahydroindole becomes available in quantity through relatively few and simple operations.

EXPERIMENTAL*

2-(2'-Nitroethyl)cyclohexanone (XVI)

This was prepared according to Reference 16 with the following modifications: only freshly distilled 2-dimethylaminocyclohexanone (b.p. 60° at 0.5 mm.) was used and vigorous stirring maintained 2-3 days under a stream of nitrogen to sweep out the dimethylamine. In this way, 90 g. of pure 2-dimethylaminocyclohexanone afforded 16.4 g. of crude product, b.p. 153-158° at 16 mm. Care must be taken not to overheat toward the end of the distillation, as vigorous decomposition of the residue takes place. Redistillation gave 13.5 g. of pure nitroketone, b.p. 104-107° at 0.35 mm. (reported (16): 154° at 14 mm.).

 $\Delta^1(7a)$ -Hexahydroindole (XVII)

The preceding 13.5 g. of 2-(2'-nitroethyl)cyclohexanone was dissolved in 100 ml. of absolute ethanol and shaken over Raney nickel under 30 lb. p.s.i. of hydrogen. Absorption ceased within 2.5 hours and after removal of the catalyst, the solvent was distilled through a short column. Distillation of the residue *in vacuo* yielded 5.80 g. of colorless base, b.p. 70°-72° at 14 mm. Calc. for $C_8H_{13}N$: N, 11.37. Found: N, 11.28. It gave a picrate separating from methanol as yellow needles, m.p. 132-133° (reported (10): 132-133°). Calc. for $C_{14}H_{16}O_7N_4$: C, 47.72; H, 4.57. Found: C, 47.85; H, 4.45.

cis-Octahydroindole

Hexahydroindole (132 mg.) in 5 ml. of absolute ethanol was hydrogenated over pre-reduced Adams' catalyst (10 mg.) at room temperature and atmospheric pressure. After 75 minutes, 98% of the theoretical amount of hydrogen was absorbed. The catalyst was filtered off, the solvent evaporated, and the base isolated as its picrate, which separated from benzene as yellow prisms, m.p. 135°-137° (19), alone or when admixed with an authentic sample prepared according to the literature (19).

Hexahydroindole (XVII) from XVIII

A solution of 20.8 g. of potassium was prepared in 500 ml. of dry *t*-butyl alcohol followed by the addition of 88.5 g. of 2-ethoxycarbonylcyclohexanone. The alcohol was distilled off, dry toluene added, and the solution distilled to remove the last traces of alcohol. Then, 500 ml. of dry toluene was added followed by 133 g. of 2-bromoethylphthalimide in 200 ml. of hot toluene. The mixture was stirred and heated under reflux for 20 hours. It was cooled, poured into water, and the toluene layer dried and evaporated. The residue was distilled *in vacuo* to yield at 115-125° and 20 mm. 38 g. of unchanged 2-ethoxycarbonylcyclohexanone. The residue was heated under reflux in a mixture of 100 ml. of acetic acid and 250 ml. of concentrated hydrochloric acid for 15 hours. The mixture was cooled and filtered to remove phthalic acid. The filtrate was concentrated to a small volume *in vacuo*, 250 ml. of water added, and the solution made strongly alkaline followed by extraction with ether. The ether was dried and evaporated and the residue distilled *in vacuo* to give 13.4 g. (37% yield based on unrecovered β -ketoester) of material identical with the above hexahydroindole. Attempts to isolate in a state of purity the intermediate alkylation product XVIII were not successful.

*All melting and boiling points are uncorrected. The microanalyses were carried out by the Schwartzkopf Microanalytical Laboratory and Messrs. B. Girard and B. Mercier of our laboratories.

Ethyl α -Cyano-2-oxocyclohexane Acetate (XIX)

To 1500 ml. of absolute ethanol was added in portions 56 g. of sodium, and to the solution was added 275 g. of ethyl cyanoacetate. The alcohol was distilled *in vacuo* and two portions of 300 ml. of benzene distilled from the residue to remove the last traces of alcohol. Two liters of dry benzene was then added and, while stirring, 248 g. of 2-chlorocyclohexanone (12) was added at a rate to maintain gentle reflux. The mixture was stirred and heated under reflux for 4 hours, cooled, and poured into water. The benzene layer was dried and evaporated and the residue distilled; at 158–160° and 2 mm. there was obtained 262 g. of XIX as a yellowish oil with a pleasant honeylike odor. The yield amounted to 66%. Calc. for $C_{11}H_{18}O_3N$: N, 6.69. Found: N, 6.72. If the condensation was carried out in alcohol instead of benzene, only intractable tars resulted. The sodio derivative of ethyl cyanoacetate could also be prepared with sodium hydride in benzene, but on the scale employed, this procedure was found hazardous, the reaction sometimes getting out of control after a long induction period.

2-Oxocyclohexaneacetonitrile (XX)

A solution of 604 g. of the preceding substance (XIX) in 1200 ml. of absolute ethanol was cooled to –15° in an ice and salt bath and, while stirring, a solution of 116 g. of sodium hydroxide in 150 ml. of water was added over a period of 3 to 4 hours. Toward the end of the addition a white crystalline precipitate separated and the solution soon solidified to a white mass. The mixture was allowed to stand at 0°–5° overnight. It was found disadvantageous to isolate the crystalline salt because of considerable losses reflected in the over-all yield. Instead, the mixture was treated in the cold with a chilled solution of 116 g. of concentrated sulphuric acid in 1 liter of water. The sodium sulphate was removed by filtration and the filtrate concentrated *in vacuo* until most of the alcohol had distilled. The residue was diluted with water and extracted with ether. The ether extract was dried and evaporated to a viscous sirup. It was found somewhat critical at this point to remove all traces of water from the residue to ensure a maximum yield in the next operation. Failure to do that decreased the yield by as much as 20–25%. Thus, benzene was distilled from the sirupy residue until the distillate was clear. About 50 g. of the residue was placed in a 1-liter three-necked flask equipped with a condenser and stirrer. While the residue was being stirred, the flask was heated to 170° whereupon decarboxylation took place; the rest of the sirup, kept at 100°, was added in a thin stream over about 1 hour while a temperature of 170° was maintained in the flask. The brown residue was distilled *in vacuo* to yield 248 g. (63% yield) of colorless 2-oxocyclohexaneacetonitrile, b.p. 137–139° at 10 mm.; it solidified to colorless plates, m.p. 25–26° (reported (6): 143–145° at 12 mm.). Calc. for $C_8H_{11}ON$: N, 10.21. Found: N, 10.30.

2-Oxocyclohexaneacetonitrile Ethylene Ketal (XXI)

The preceding ketonitrile (XX), 231 g., was mixed with 108 g. of pure ethylene glycol, 500 ml. of benzene, and 1 g. of *p*-toluenesulphonic acid (if too small an amount of *p*-toluenesulphonic acid is used, the reaction becomes very sluggish and ketalization is incomplete). The mixture was heated under reflux with a Dean-Stark water separator. Within 2 hours, the theoretical amount of water had separated (about 30 ml.) and the cooled mixture was washed with dilute alkali, and the benzene layer dried and evaporated. Distillation of the residue afforded 290 g. (95% yield) of colorless liquid, b.p. 138–140° at 10 mm. Calc. for $C_{10}H_{18}O_2N$: N, 7.76. Found: N, 7.71.

Hexahydroindole (XVII) from XXI

To a solution of 12 g. of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran was added dropwise and while stirring 36 g. of the preceding nitrile-ketal (XXI) in 50 ml. of tetrahydrofuran. The mixture was heated under reflux for 5 hours, after which time the solvent was removed under reduced pressure and replaced by 250 ml. of ether. The excess hydride was decomposed carefully with 13 ml. of water followed by 10 ml. of 20% aqueous sodium hydroxide and then 45 ml. of water. The precipitated salts were removed by filtration and the filtrate extracted with dilute hydrochloric acid. The acid extract was allowed to stand 1 hour, then made strongly alkaline and extracted with ether. The ether was dried and evaporated and the residue distilled *in vacuo* to give 17.0 g. (68% yield) of colorless hexahydroindole, b.p. 62–64° at 9 mm. If ether was used as the solvent for the reduction, the yield dropped to 30%.

Catalytic Hydrogenation of XXI to XVII

A solution of 30.0 g. of 2-oxocyclohexanecetonitrile ethylene ketal (XXI) in 250 ml. of absolute ethanol was hydrogenated over Raney nickel (2 teaspoonfuls) under 50 lb. p.s.i. of hydrogen. Two molar equivalents of hydrogen was absorbed in 4–5 hours after which time absorption ceased. The catalyst was removed by filtration and the filtrate evaporated to a liquid which was distilled *in vacuo*; at 147–148° at 24 mm. there was obtained 24.0 g. (78% yield) of colorless 2-oxocyclohexanethylamine ethylene ketal which formed a solid carbonate on standing in air. Its neutral equivalent was 186 (theory requires 185). Calc. for $C_{10}H_{19}O_2N$: N, 7.56. Found: N, 7.50. A solution of 8.90 g. of the amine-ketal was allowed to stand 1 hour in 100 ml. of 5% aqueous hydrochloric acid. The solution was made strongly alkaline and extracted with ether. The ether was dried and evaporated, followed by distillation of the residue to give 5.0 g. (84% yield) of hexahydroindole, b.p. 86° at 24 mm. The over-all yield was 65%.

Catalytic Hydrogenation of XX to XVII

When 2-oxocyclohexanecetonitrile (IX) was hydrogenated over Raney nickel in ethanol under 50 lb. p.s.i. of hydrogen, absorption was rapid, and when the reaction was allowed to proceed to completion, it was found that hexahydroindole was produced but appeared to be contaminated by octahydroindole from which separation by distillation was not possible. No attempt was made to quantitatively determine the relative proportions of the two although fractional crystallization of their picrates from methanol and benzene (octahydroindole picrate is soluble in methanol but insoluble in cold benzene whereas hexahydroindole picrate is insoluble in cold methanol) served to establish their presence as a mixture.

However, if hydrogenation was stopped after only 25% of the theoretical amount of hydrogen had been absorbed and the products separated by distillation, there was obtained pure hexahydroindole (5.80 g. from 30 g. XX) followed by unchanged ketonitrile (XX) (18.0 g. recovered from 30 g.); the yield of hexahydroindole was 53% based on unrecovered ketonitrile. The purity of the base was ascertained by quantitative hydrogenation over Adams' catalyst whereupon 98% of the theoretical amount of hydrogen was absorbed.

1-Homoveratryl-2,3,4,5,6,7-hexahydroindole

A mixture of 7.30 g. of homoveratryl bromide (b.p. 120–125° at 0.5 mm.) and 3.60 g. of hexahydroindole was heated to 100°. Within a few minutes, the mixture solidified.

The crystals were suspended in dry ether and collected on a filter. However, the product was too hygroscopic for adequate characterization. It was decomposed with excess alkali and the free base isolated in the usual way. It distilled at 165–170° at 0.4 mm. (yield 5.0 g.). It darkened when left standing in the air and failed to give crystalline salts. Calc. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.42. Found: C, 75.15; H, 8.36. It was also refractory to cyclization conditions in phosphoric or sulphuric acid.

2-(2'-Phenylacetamidoethyl)cyclohexanone (VII)

Hexahydroindole (3.08 g., 0.025 mole) was treated at 0° in 20 ml. of 7.5% aqueous sodium hydroxide with phenylacetyl chloride (4.65 g., 0.03 mole) in the usual fashion. There was isolated 6.20 g. of an oil which crystallized to small colorless needles from hexane, m.p. 53–54° (5.20 g. or 80% yield). This material exhibited peaks in the infrared region at 2.92 μ , 5.85 μ , 6.02 μ , 6.60 μ , and 6.70 μ (chloroform) in complete agreement with expectations. Calc. for $C_{16}H_{21}O_2N$: C, 74.09; H, 8.16. Found: C, 73.96; H, 8.18.

8-Oxoerythrinane (XI)

A solution of 25 g. of phosphorus pentoxide in 25 g. of 85% orthophosphoric acid was prepared, and 5.0 g. of the preceding amide (VII) added; the solution was heated to 100° for 15 to 20 hours, then diluted with water, and the mixture extracted with chloroform. The extract was washed with dilute alkali, dried, and evaporated to yield an oil which crystallized from ethyl acetate in the shape of large prisms, m.p. 130–133° (2.80 g. or 60% yield). The analytical sample had m.p. 132–133° and exhibited a peak in the infrared region at 6.14 μ (chloroform). Calc. for $C_{16}H_{19}ON$: C, 79.62; H, 7.93; N, 5.80. Found: C, 79.71; H, 8.02; N, 5.62. It was recovered unchanged in quantitative yield after protracted heating in 10% alcoholic sodium hydroxide or concentrated hydrochloric acid.

Oxidative Degradation of 8-Oxoerythrinane (XI)

A solution of 500 mg. of XI in 40 ml. of nitric acid ($d = 1.42$) was heated under reflux for 20 hours. The nitric acid was distilled *in vacuo*, the residue extracted with ether, and the extract washed with water, dried, and evaporated to a sirup. A little acetic anhydride was added and distilled from the sirup, which was then carefully heated over a free flame in a sublimation apparatus. The oily sublimate was triturated with ether, whereupon crystallization occurred. The crystals were resublimed *in vacuo* (1 mm.) and twice recrystallized from anhydrous ether to give cream-colored leaflets, m.p. 116–119° (yield 51 mg.). When admixed with an authentic sample of 4-nitrophthalic anhydride of m.p. 117–119°, no depression of the m.p. was observed. About 15 mg. of the anhydride was boiled for a few minutes with 3 drops of aniline in a little toluene. A solid separated which was recrystallized from methanol to give cream-colored leaflets, m.p. 198°. This m.p. was not depressed when the product was admixed with an authentic specimen of 4-nitrophthalanil, itself melting at 197–198°.

Erythrinane (XIII)

A mixture of 2.0 g. of 8-oxoerythrinane and 1 g. of lithium aluminum hydride in 150 ml. of dry ether was heated under reflux for 5 hours, after which time the excess hydride was decomposed with ethyl acetate followed by hydrolysis with water. The ethereal layer was extracted with dilute hydrochloric acid and the acid extract made alkaline and extracted with ether. Evaporation of the ether gave an oil which when treated in

ether with dry hydrogen chloride yielded 1.72 g. of a crystalline hydrochloride. Recrystallization from acetone afforded colorless needles of erythrinane hydrochloride, m.p. 275° (decomp.) (shrinks over 200°). Calc. for $C_{16}H_{22}NCl$: C, 72.84; H, 8.40. Found: C, 72.81; H, 8.45. Erythrinane also formed a picrate separating as yellow blades from methanol, m.p. 184–185°. Calc. for $C_{22}H_{24}O_7N_4$: N, 12.27. Found: N, 12.29. It gave a crystalline methiodide separating as colorless prisms from ethyl acetate–acetone, m.p. 201–203°. Calc. for $C_{17}H_{24}NI$: I, 34.3. Found: I, 34.1.

2-(2'-Homoveratramidoethyl)cyclohexanone (VIII)

Ten grams of 3,4-dimethoxyphenylacetic acid in 50 ml. of benzene was treated with 10 g. of pure thionyl chloride at 50–60° for 1 hour. The benzene was evaporated *in vacuo* and more benzene added and distilled from the residue. The oil was dissolved in 50 ml. of dry benzene and the solution added dropwise to a stirred mixture of 7.3 g. of hexahydroindole, 50 ml. of benzene, and 50 ml. of 12% aqueous sodium hydroxide. Working up in the usual way gave an oil which crystallized from ethyl acetate–ether as fine colorless needles, m.p. 89–90° (crystalline change at 85°). The yield amounted to 15.0 g. (93% yield). Calc. for $C_{18}H_{26}O_4N$: C, 67.68; H, 7.89. Found: C, 67.61; H, 7.92.

2,3-Dimethoxy-8-oxoerythrinane (XII)

To a solution of 50 g. of phosphorus pentoxide in 50 g. of sirupy phosphoric acid was added 9.0 g. of the preceding ketoamide (VIII) and the mixture stirred at 100° for 3 hours. It was cooled and worked up as above in the case of XI. There was obtained 5.40 g. (71% yield) of colorless crystals, m.p. 156–158°. Two recrystallizations from ethyl acetate–ether afforded colorless prisms, m.p. 158–159°. On recrystallization it occasionally gives crystals of m.p. 147–148°. This low-melting form is reconverted to the high-melting one by seeding with crystals of m.p. 159° and vice versa. Calc. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.35; N, 4.67. Found: C, 71.78; H, 7.30; N, 4.77.

DL-Hexahydroapoerysotrine (XIV)

A solution of 5.10 g. of 2,3-dimethoxy-8-oxoerythrinane (XII) in 30 ml. of dry tetrahydrofuran was added slowly to a solution of 2.5 g. of lithium aluminum hydride in 125 ml. of tetrahydrofuran. After heating under reflux for 4 hours, it was decomposed and worked up as above in the case of erythrinane (XIII). Treatment of the base in ether with dry hydrogen chloride afforded 3.10 g. of crystals, which upon recrystallization from acetone gave colorless needles, m.p. 225–227° (decomp.). Calc. for $C_{18}H_{26}O_2NCl$: N, 4.32; Cl, 10.94. Found: N, 4.38; Cl, 11.03. The base also gave a picrate separating from methanol as yellow prisms, m.p. 186–189°, or small rods, m.p. 170–172°. Both forms are interconvertible by cross-seeding and had an identical infrared spectrum which also proved indistinguishable from the spectrum of an authentic sample of hexahydroapoerysotrine picrate in chloroform solution. Calc. for $C_{24}H_{28}O_9N_4$: C, 55.80; H, 5.46; N, 10.85. Found: C, 55.67; H, 5.24; N, 10.81.

(—)-Hexahydroapoerysotrine

A solution of 0.713 g. of pure dimethoxyerythrinane (regenerated from its purified crystalline hydrochloride) in ethyl acetate was treated with a solution of 0.934 g. of dibenzoyltartaric acid in ethyl acetate. The mixture was chilled overnight and the crystalline precipitate collected. After four recrystallizations from acetone (containing a few drops of methanol) it afforded 492 mg. of large, colorless flat needles with a constant

m.p. of 133–133.5°. Calc. for $C_{36}H_{39}O_{10}N$: C, 66.96; H, 6.08. Found: C, 66.76; H, 6.25. The free base was regenerated from its dibenzoyltartrate and treated with picric acid in methanol to give yellow crystals (325 mg.) which upon recrystallization from methanol afforded yellow prisms, m.p. 205–207° (reported (14): 205–206°). When admixed with the authentic specimen obtained from Professor V. Prelog, no depression of the m.p. was obtained. Calc. for $C_{24}H_{28}O_9N_4$: C, 55.80; H, 5.46. Found: C, 55.88; H, 5.28. The infrared spectra of chloroform solutions of the two picrates were identical. The regenerated base from its pure picrate had $[\alpha]_D^{24} = -43 \pm 3^\circ$, (ethanol); (reported (14): $[\alpha]_D^{21} = -39 \pm 3^\circ$ (ethanol)).

1,1-Pentamethylene-3-oxo-1,2,3,4-tetrahydroisoquinoline (XV)

A mixture of 6 g. of phenylacetamine, 4.5 g. of cyclohexanone, and 140 g. of equal weights of phosphorus pentoxide and phosphoric acid was heated to 100° for 10 hours; it was worked up in the usual way and the crude product extracted with boiling concentrated hydrochloric acid which was decanted while hot from an insoluble gum. The clear extract was diluted, whereupon white crystals separated. Recrystallization from methanol afforded 3.2 g. of colorless blades, m.p. 176–178°. Calc. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.41; H, 8.11; N, 6.42. The product was recovered unchanged after protracted heating in concentrated hydrochloric acid. It exhibited a maximum at 265 $m\mu$ ($\log \epsilon$, 2.6) in the ultraviolet region.

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SYNTHESIS IN THE FIELD OF THE ERYTHRINA ALKALOIDS

PART II. APPROACHES TO THE RING SYSTEM OF β -ERYTHROIDINE¹

B. BELLEAU

ABSTRACT

The newly developed method for the elaboration of the ring system of the aromatic class of *Erythrina* alkaloids has been successfully extended to the synthesis of 1,2,3,4-tetrahydro-erythrinane (VI), a non-aromatic analogue. The key step in this synthesis involves ring closure of ketoamide (IV) itself, obtained from hexahydroindole and cyclohexenylacetic acid. Attempts to further extend this sequence to the use of 2H-5,6-dihydropyranacetic acid as starting material met with failure at the stage of preparation of the latter. A new and unrelated stepwise approach illustrated on Chart III was investigated but failed at the ultimate step. Other unsuccessful approaches are also briefly described.

The complete structure elucidation of β -erythroidine (I), the most important member of the non-aromatic class of *Erythrina* alkaloids, was reported by Boekelheide and his collaborators (4). The essential features of this brilliant investigation have been reviewed recently by Boekelheide (3) and it may be pertinent to recall that by demethoxylation and hydrogenation it was possible to convert β -erythroidine to demethoxyhexahydro- β -erythroidine (II) in which the ring system of the original alkaloid is retained. Further reduction of II with lithium aluminum hydride afforded demethoxyhexahydro- β -erythroidinol (III), a cleavage product of II. It is the purpose of this communication to describe synthetic approaches to any of those two unrearranged transformation products of β -erythroidine.

In a preceding communication, the successful synthesis of the intact ring system (1) of the aromatic *Erythrina* alkaloids was reported. It was of interest at first to explore the possibility of extending our findings in the field of the aromatic series of alkaloids to the synthesis of hydroaromatic analogues, with the hope that subsequent appropriate variations might lead to a synthesis of either II or III or both. In view of Grewe's success (8) in substituting cyclohexenyl ethylamine for the usual phenethylamines in the classical Pictet-Spengler synthesis, it was logical in a parallel mode of reasoning to expect cyclohexenylacetamide derivatives to be similarly cyclizable, especially because of our previous success with arylacetamide derivatives (1). In a preliminary investigation, this presumption was indeed verified and the successful condensation of N-methyl cyclohexenylacetamide with formaldehyde is included in a separate report (2). By analogy, the ketoamide (IV) obtainable from cyclohexenylacetyl chloride and hexahydroindole would be expected to ring close to the tetracyclic spiroamide (V) under acid conditions. In fact, when the oily ketoamide (IV) was heated in polyphosphoric acid for several hours, there was obtained in good yield an oily amide analyzing correctly for V. Although its structure has not been rigorously established, it can be strongly inferred that V is the correct one on the basis of its refractoriness to alkaline hydrolysis coupled with an infrared absorption band at 6.10μ characteristic of a disubstituted amide carbonyl (unconjugated). Mechanistic considerations also point to V as the best possibility. Reduction of V with lithium aluminum hydride readily gave the corresponding base (VI), which formed crystalline salts.

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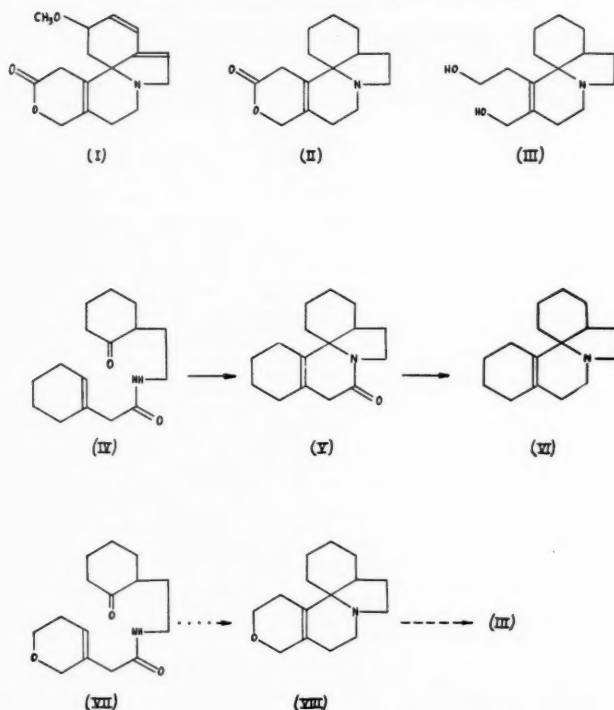


CHART I.

With these results on hand, it became of interest to attempt the extension of this sequence to a suitable heterocyclic acetamide derivative such as VII which should ultimately be convertible to the known demethoxyhexahydro- β -erythroidinol (III). For this purpose, 2H-5,6-dihydropyranacetic acid (XII) was required and its preparation attempted. The acid dimerization product of acrolein (IX) (7), whose structure has been recently confirmed by Hall (9), was chosen as starting material. Reduction of IX with sodium borohydride afforded the expected alcohol (X) in high yield, which was treated with thionyl chloride followed by reaction with cuprous cyanide to give 2H-5,6-dihydropyran-3-acetonitrile (X) in good over-all yield. When the latter was submitted to alkaline hydrolysis, a nitrogen-free and homogeneous neutral substance was obtained as the only product. Its behavior towards aqueous alkali clearly indicated it to be a lactone for which structure XIII is the only one acceptable. In fact, the β,γ -unsaturated acid XIV, which can undoubtedly be formed from X during the course of hydrolysis, would be expected to lactonize spontaneously in view of the well-known reactivity of dihydropyran towards acids. It is clear that alkali must have caused migration of the double bond to give XIV and it can be expected that this type of isomerization in the dihydropyran series is most probably irreversible. In another attempt to secure a sample of the acid (XII), the nitrile (X) was submitted to methanolysis to give the expected methyl ester (XI) followed by treatment with cold potassium carbonate. Again, lactone (XIII) was the only product. Mild acid hydrolysis of XI also failed to produce the acid (XII), the

reaction being presumably complicated by the acid sensitivity of the allylic ether bond. This approach was set aside at this point because of other seemingly promising routes.

Another possible approach centered about the tricyclic ketone (XXII) which theoretically appeared accessible by well-established methods and from which it may be possible

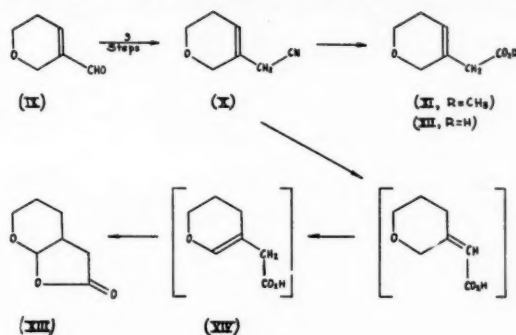


CHART II.

to construct an unsaturated lactone of the type present in β -erythroidine. As starting material, hexahydroindole (I) was chosen and the first problem consisted in converting it to the amino acid ester (XVIII) through the aminonitrile (XV) as an intermediate. However, even though hexahydroindole reacted readily with hydrogen cyanide, subsequent acid hydrolysis always led to quantitative recoveries of hexahydroindole. This reversal of aminonitrile synthesis has since been found to be general when the amine is secondary or tertiary with the exception of aromatic amines, and it is hoped to discuss this work separately in a future publication. As an alternative, hexahydroindole was first quaternized with methyl 4-bromobutyrate to give XVI, which also failed to give a stable adduct when reacted with potassium cyanide. In order to circumvent these difficulties, recourse was made to the observations of Cobb and McEwen (5) in connection with their mechanism studies on the hydrolysis of Reissert's compounds. They showed that there exists a strong interaction between the amide carbonyl and nitrile groups of quinaldonitrile benzoate and consequently that the amide carbonyl group participates in the hydrolysis of the nitrile group. Accordingly, if the nitrile benzoate (XVII) could be obtained, a similar participation of the amide carbonyl group might occur and it is conceivable that the first step in the hydrolysis of XVII might be over-all addition of one molecule of water to give the amide (XVIIc) as pictured in formula XVIIa and XVIIb. Reversal to hexahydroindole would obviously be impossible upon subsequent removal of the benzoyl group. Consequently, hexahydroindole was reacted with benzoyl chloride in the presence of sodium cyanide with anhydrous hydrogen cyanide as the solvent to give a single isomer of the desired nitrile benzoate (XVII) in high yield. Acid hydrolysis of the latter followed by esterification of the crude hydrolyzate finally afforded the desired methyl ester (XVIII) in good over-all yield. Alkylation of the latter with methyl 4-bromobutyrate proceeded smoothly to give XIX, which underwent ready Dieckman ring closure to a single isomer of the tricyclic β -ketoester (XX). It was hoped from there that the introduction of an acetic acid residue onto the carbonyl group might be accomplished, in which case subsequent reduction would have led to demethoxy- β -erythroidinol (III). However, all attempts at condensing the ketoester (XX) with

either ethyl cyanoacetate or malononitrile following Cope's directions (6) were fruitless, starting material being recovered unchanged. This failure is undoubtedly ascribable to prohibitive steric hindrance about the carbonyl group.

As an alternative approach, the β -ketoester (XX) was submitted to acid hydrolysis, whereupon the tricyclic ketone (XXII) was formed in excellent yield. This ketone is

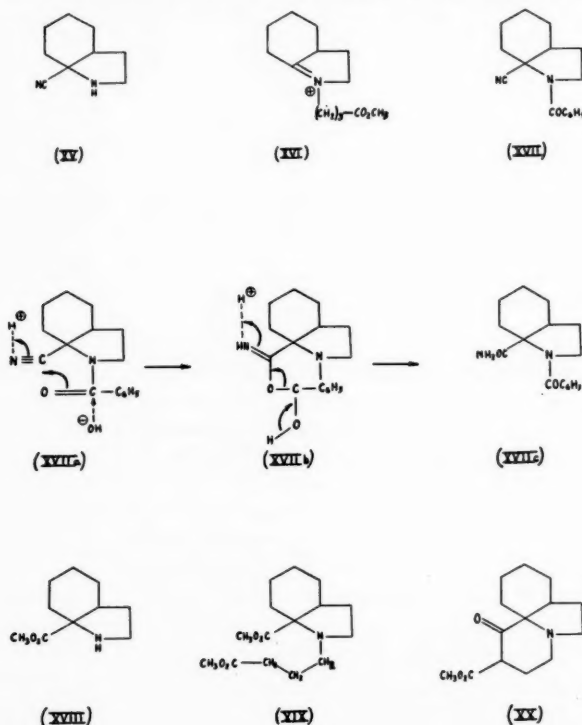


CHART III.

also hindered since it failed to react with phenylhydrazine. Nevertheless, it was of interest to attempt the introduction of an acetic acid residue onto this carbonyl group through the use of ethoxyacetylene magnesium bromide (10) in view of the extremely small molecular volume of the acetylene carbanion, a fact that should minimize steric inhibition of approach to the carbonyl carbon. Indeed, this reaction gave an oily adduct (XXIII), which without purification was rearranged with acid followed by saponification in the usual manner (10) to give an amorphous amino acid hydrochloride in about 40% over-all yield. The latter was shown to be homogeneous as judged by paper chromatography and paper electrophoresis even though no reliable elementary analysis could be performed presumably because of its hygroscopic character. Nevertheless, being transparent in the ultraviolet region up to 205 $\text{m}\mu$, it was assumed that the unconjugated amino acid (XXIV) was on hand and our newly developed procedure for the synthesis of unsaturated δ -lactones (2) directly applied to the crude product (XXIV). In this manner, treatment of the amino acid with paraformaldehyde in trifluoroacetic acid afforded a homogeneous

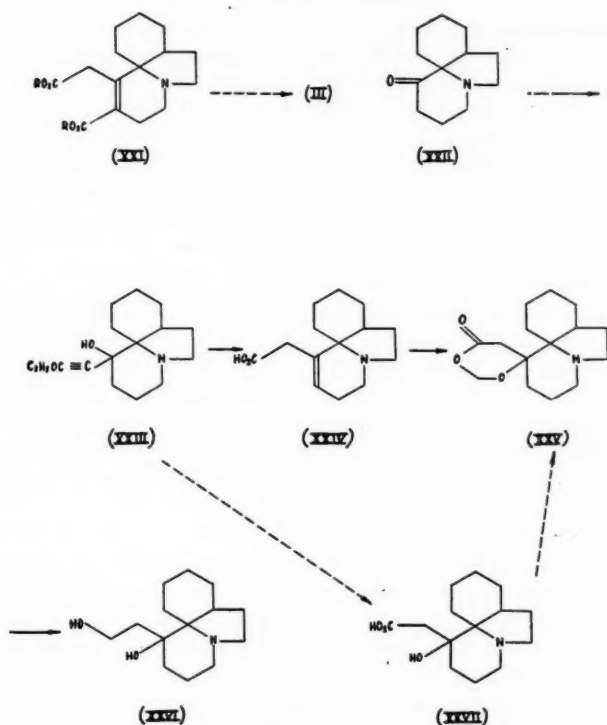


CHART IV.

crystalline substance, m.p. 98° , in about 35% yield (based on unrecovered starting material) which from its elementary composition ($C_{15}H_{23}O_3N$) contained one more oxygen atom than required by demethoxyhexahydro- β -erythroidine (II), the expected final product. Quite revealing was the infrared spectrum of this crystalline product, which showed a strong band at 1770 cm^{-1} normally attributable to a saturated γ -lactone grouping. In agreement with a lactone structure, the product dissolves in warm aqueous alkali but, *in conflict with a γ -lactone structure, it cannot be recovered from the acidified solution*. It seems therefore that not only does the lactone grouping suffer opening in the presence of alkali but that some element essential to its existence is actually destroyed by it. These facts taken together with theoretical considerations agree with a structure such as XXV, which provides for the irreversible opening of the lactone ring by virtue of the loss of the elements of formaldehyde. There remains to explain the infrared absorption at 1770 cm^{-1} , which is in conflict with the δ -lactone structure (XXV). It has been shown (11) that in 1,1-diacetoxyp propane, the ester carbonyl band appears at 1761 cm^{-1} instead of 1740 cm^{-1} where it should normally appear. Since structure XXV is in fact a cyclic hemiacetal ester in which the carbonyl group is in a similar situation as in propylidene acetate, a shift to lower frequencies would then be expected. On that basis, structure XXV becomes logical, and in agreement with this formulation, lithium aluminum hydride reduction led in high yield to a crystalline diol analyzing correctly for a $C_{14}H_{26}O_2N$ formula (XXVI).

Since the amorphous amino acid used as starting material in this last step could not be adequately characterized as yet, further comments on the structure and mechanism of formation of lactone (XXV) are deferred. It is conceivable in spite of the chromatographic evidence that the amorphous amino acid actually contained some hydroxyamino acid (XXVII) which would best account for the production in low yield of lactone (XXV).

It is hoped to publish elsewhere the pharmacological properties of several of the intermediates.

EXPERIMENTAL*

2-(2'-Cyclohexenylacetamidoethyl)cyclohexanone (IV)

An ethereal solution of cyclohexenylacetic acid (12 g.) was treated with 12 ml. of thionyl chloride; the solution was heated under reflux for 1 hour and the acid chloride purified by distillation *in vacuo*; yield 10 g., b.p. 75° at 10 mm. Cyclohexenylacetyl chloride (6.90 g.) in a little ether was reacted with hexahydroindole (5.11 g.) under the usual Schotten-Baumann conditions. There was obtained 10.5 g. of an oily amide which proved resistant to crystallization. It was filtered in benzene through activated alumina prior to analysis. Calc. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.56. Found: C, 72.60; H, 9.71.

1,2,3,4-Tetrahydro-8-oxoerythrinane (V)

To a solution of 80 g. of phosphorus pentoxide in 80 g. of sirupy phosphoric acid was added 10 g. of the preceding oily ketoamide and the mixture kept at 100° for 20 hours. It was worked up in the usual way to yield a viscous oil which failed to crystallize. It was purified by heating under reflux in excess methanolic potassium hydroxide for 15 hours followed by extraction with ether of the insoluble material. This yielded 5.67 g. of a yellow viscous oil which was further purified by evaporative distillation *in vacuo* at a bath temperature of 180–200° at 0.5 mm. This material gave satisfactory analytical figures. Calc. for $C_{16}H_{23}ON$: C, 78.32; H, 9.44. Found: C, 78.10; H, 9.61.

1,2,3,4-Tetrahydroerythrinane (VI)

A mixture of 5.0 g. of the preceding lactam (V) and 4 g. of lithium aluminum hydride in 250 ml. of dry ether was heated under reflux for 4 hours, the excess hydride was decomposed with ethyl acetate, and the base extracted from the ether with dilute hydrochloric acid. The acid extract was made alkaline and extracted with ether and the extract dried and evaporated. The residual oil was treated with 50 ml. of hot ethanol containing 5.5 g. of picric acid. On cooling, 3.65 g. of golden blades separated and had m.p. 175–180°. Recrystallization from methanol raised the m.p. to 178.5–180.5°. Calc. for $C_{22}H_{28}O_7N_4$: C, 57.38; H, 6.12; N, 12.16. Found: C, 57.47; H, 6.02; N, 11.98. The base was regenerated from its picrate and converted to a crystalline hydrochloride which separated from acetone as fine colorless needles, m.p. 233–235° (crystalline change at 160° and shrinking at 225°). Calc. for $C_{16}H_{26}NCl$: C, 71.74; H, 9.78. Found: C, 71.83; H, 9.65.

2H-5,6-Dihydropyran-3-carboxaldehyde (IX)

This was prepared according to Geyer and Mortimer (7) except that neutralization of the acid at the end of the reaction was accomplished more conveniently with sodium

*All boiling and melting points are uncorrected. Microanalyses by the Schwartzkopf Microanalytical Laboratory and Messrs. B. Mercier and B. Girard of our laboratories.

bicarbonate instead of basic lead carbonate. The yield of twice-distilled aldehyde (b.p. 88–90° at 16 mm.) was 20%. Its 2,4-dinitrophenylhydrazone had m.p. 233–234° (reported (9): 234–235°).

2H-5,6-Dihydropyran-3-methanol

To a solution of 9.0 g. of sodium borohydride in 100 ml. of 80% aqueous ethanol was added in portions 40 g. of the preceding 2H-5,6-dihydropyran-3-carboxaldehyde with intermittent cooling. The mixture was allowed to stand overnight and the alcohol evaporated on the steam bath. The residue was extracted with ether and the solution dried, filtered, and evaporated. Distillation of the residue *in vacuo* afforded 35.0 g. of colorless liquid, b.p. 112–114° at 15 mm. Calc. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.06; H, 8.91.

3-Chloromethyl-2H-5,6-dihydropyran

The preceding 35 g. of 2H-5,6-dihydropyran-3-methanol in 60 ml. of chloroform and 24 g. of pyridine at 0° was treated over 1 hour with 37 g. of thionyl chloride. The solution was stirred at 0° an additional 30 minutes after which time it was poured into cold water and extracted with ether. The extract was washed with cold dilute sodium hydroxide, then dried and evaporated. The residue was distilled *in vacuo* to give at 75–80° and 14 mm. 27.3 g. of colorless liquid which is very irritating to the eyes. Calc. for C_6H_9OCl : Cl, 26.77. Found: Cl, 26.82.

2H-5,6-Dihydropyran-3-acetonitrile (X)

Twenty-seven grams of the preceding chloride was mixed with 40 g. of cuprous cyanide and 100 ml. of xylene. The mixture was stirred and heated under reflux for 8 hours, then cooled, and the solvent decanted from a black tar. Evaporation *in vacuo* followed by distillation afforded 10 g. of a colorless liquid, b.p. 120–122° at 18 mm. Calc. for C_7H_9ON : N, 11.37. Found: N, 11.34.

2-Hydroxyl-tetrahydropyran-3-acetic Acid Lactone (XIII)

Nine grams of the preceding nitrile (X) was heated under reflux in ethanolic potassium hydroxide for 20 hours; the alcohol was removed by distillation, the residue diluted with water, and, after one ether wash, it was carefully acidified to litmus and extracted with ether. The ether extract was dried and evaporated and the residue distilled *in vacuo*; at 86–88° and 0.2 mm. there was obtained 5.80 g. of a colorless neutral distillate. Its saponification equivalent was 141 (theory, 142). It decolorized bromine in carbon tetrachloride with copious evolution of hydrogen bromide and gave no color with tetranitromethane. Calc. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.22; H, 7.20.

Methyl 2H-5,6-Dihydropyran-3-acetate

The above nitrile (X), 27.5 g., was mixed with a cold solution of 22 g. of concentrated sulphuric acid in 100 ml. of dry methanol. The solution was allowed to stand for 24 hours after which time 4 ml. of water was added followed by heating under reflux for 2 hours. The mixture was concentrated *in vacuo*, diluted with ice water, and extracted with ether. The extract was dried and evaporated and the residue distilled; at 103–105° and 6 mm. there was obtained 20.0 g. of colorless distillate. Calc. for $C_8H_{12}O_3$: C, 61.61; H, 7.74. Found: C, 61.63; H, 7.60.

Methyl 2,3,4,5,6,7-Hexahydroindole-1-butyrate and Its Quaternary Bromide (XVI)

Equimolar amounts of hexahydroindole and methyl 4-bromobutyrate were heated to 100°. A very exothermic reaction took place spontaneously and required cooling. Within a few minutes, the mixture completely solidified. The crystals were suspended in dry ether and collected under dry nitrogen. The yield was quantitative and the product very hygroscopic. On treatment with cold aqueous potassium cyanide in the usual way, an oil separated, which on distillation *in vacuo*, yielded in almost quantitative yield a colorless liquid, b.p. 150–153° at 11 mm. Calc. for $C_{13}H_{21}O_2N$: C, 69.91; H, 9.48. Found: C, 70.05; H, 9.55.

1-Benzoyl-7a-cyano-octahydroindole (XVII)

To a solution of 15.4 g. of hexahydroindole in 40 ml. of anhydrous hydrogen cyanide at -15° was added 6.3 g. of powdered sodium cyanide, and dropwise, while stirring, 18.3 g. of benzoyl chloride in 35 ml. of dry ether was introduced over a period of 45 minutes. Stirring was continued an additional 45 minutes, and the excess hydrogen cyanide swept out with nitrogen. The mixture was quenched with ice water and the crystalline mass that separated was collected. Recrystallization from methanol afforded colorless thick blades, m.p. 148.5–149.5°. The yield of pure material was 29.1 g. Calc. for $C_{16}H_{18}ON_2$: C, 75.55; H, 7.13; N, 11.01. Found: C, 75.58; H, 7.21; N, 11.08.

7a-Methoxycarbonyl-octahydroindole (XVIII)

The preceding nitrile (XVII), 27.9 g., was heated under reflux in 250 ml. of concentrated hydrochloric acid for 18 hours. The solution was cooled, one volume of water added, and the benzoic acid removed by filtration. The filtrate was twice washed with ether and evaporated to dryness *in vacuo*. The solid residue was dissolved in 300 ml. of dry methanol containing 25 ml. of concentrated sulphuric acid and the solution heated under reflux for 15 hours. About half of the solvent was evaporated and the solution poured into water. After one ether wash, the aqueous phase was made alkaline with cold sodium hydroxide solution and extracted with ether. The ether extract was dried and evaporated and the residue distilled *in vacuo*; at 60–80° and 12–13 mm. there was recovered 7.50 g. of crude hexahydroindole followed by 8.40 g. of XVIII as a colorless liquid, b.p. 100–101° at 10 mm. The latter was characterized as its crystalline hydrochloride which separated from methanol-acetone as small colorless needles, m.p. 183–184° (decomp.). Calc. for $C_{10}H_{18}O_2NCl$: N, 6.37; Cl, 16.18. Found: N, 6.41; Cl, 16.11. Its picrate separated from methanol as yellow prisms, m.p. 174–175°. Calc. for $C_{16}H_{20}O_5N_4$: N, 13.58. Found: N, 13.52.

Methyl 7a-Methoxycarbonyl-1-octahydroindolebutyrate (XIX)

The above 7a-methoxycarbonyl-octahydroindole, 6.22 g., was mixed with 6.4 g. of methyl 4-bromobutyrate and 2.4 g. of anhydrous potassium carbonate in 15 ml. of methanol. The mixture was heated under reflux for 18 hours after which time 5.0 g. of methyl 4-bromobutyrate and 2.8 g. of potassium bicarbonate were added and the reflux resumed for 6–8 hours. The solution was diluted with water and extracted with ether. The extract was dried and evaporated and the residue distilled *in vacuo* to give at 170–173° and 8 mm. 5.48 g. of colorless diester (XIX). It gave a crystalline hydrochloride separating from acetone as colorless rods, m.p. 150–151° (decomp.). Calc. for $C_{15}H_{26}O_4NCl$: N, 4.38; Cl, 11.08. Found: N, 4.25; Cl, 11.17. The picrate was obtained from methanol

as yellow parallelograms, m.p. 127–128°. Calc. for $C_{21}H_{23}O_{11}N_4$: N, 10.93. Found: N, 11.04.

1,11-Ethylene-4-methoxycarbonyl-1-azaspiro[5,5]undecane-5-one (XX)

Fresh sodium methoxide was prepared from 1.40 g. of sodium in a little absolute methanol and dried at 100° under 1 mm. To the dried powder was added 4.18 g. of the preceding diester (XIX) in 75 ml. of dry xylene. The mixture was heated under reflux under dry nitrogen for 90 minutes, after which time 30–40 ml. of xylene was allowed to distill over an additional hour. The mixture was cooled and poured into dilute hydrochloric acid, and the acid solution neutralized with aqueous potassium carbonate and extracted with ether. The ether was dried and evaporated to a viscous oil which was treated with dry hydrogen chloride in ether, whereupon 3.65 g. of white crystals, m.p. 170–175°, separated. Recrystallization from acetone afforded colorless prisms, m.p. 174° (decomp.). This material gave a deep purple color with alcoholic ferric chloride. Calc. for $C_{14}H_{22}O_3NCl$: N, 4.86; Cl, 12.32. Found: N, 4.78; Cl, 12.41. All attempts at condensation of the base with malononitrile or cyanoacetic ester using ammonium acetate as the catalyst led only to unchanged starting material.

1,11-Ethylene-1-azaspiro[5,5]undecane-5-one (XXII)

One gram of the preceding ketoester hydrochloride was heated under reflux for 5 hours in 50 ml. of concentrated hydrochloric acid. The solution was taken to dryness *in vacuo*, the residue shaken with excess aqueous alkali and extracted with ether. The ether extract was dried, concentrated, and treated with dry hydrogen chloride, whereupon 640 mg. of crystals, m.p. 184–188°, separated. Recrystallization from acetone afforded colorless cubes, m.p. 186–187° (decomp.). This material gave no coloration with alcoholic ferric chloride. Calc. for $C_{12}H_{20}ONCl$: N, 6.09; Cl, 15.43. Found: N, 6.13; Cl, 15.52. The base was recovered unchanged after protracted heating with excess phenylhydrazine in methanol.

1,11-Ethylene-1-azaspiro[5,5]undec-4-ene-5-acetic Acid (XXIV)

A benzene solution of ethoxyacetylene magnesium bromide was prepared in the usual way from 1.90 g. of ethoxyacetylene (10) and propylmagnesium bromide itself, obtained from 1.13 g. of magnesium and 5.80 g. of propyl bromide. To this was added 5.50 g. of pure oily ketone (XXII) in 25 ml. of benzene and the mixture stirred at room temperature for 5 hours. A viscous brown oil slowly separated. The mixture was treated with saturated ammonium chloride solution followed by extraction with chloroform. The extract was dried and evaporated and the residue treated at reflux temperature for 1 hour with aqueous alcoholic hydrogen chloride (10% solution). After it had been standing for 2 days, the solution was taken to dryness *in vacuo* and the residue treated for 1 hour with excess 10% alcoholic sodium hydroxide at the boiling point. The solution was concentrated *in vacuo*, diluted with water, and washed with several portions of ether which removed some neutral material that was not further investigated. The washed aqueous phase was filtered through a column of Amberlite IRA-400 in basic form and the column washed with water until the eluate was neutral. The product was eluted with 2% hydrochloric acid and the eluate evaporated to dryness *in vacuo* under a carbon dioxide atmosphere. The residue was a yellow sirup weighing 2.13 g. which failed to crystallize or to yield crystalline derivatives. It was freely soluble in water and aqueous alkali. Paper chromatography using 80% aqueous pyridine and dilute permanganate as the developer

revealed it to be homogeneous as judged by the appearance of a single sharp spot with R_F 0.64. Paper electrophoresis at pH 8.5 also gave a single sharp band with a mobility characteristic of monoamino-monocarboxylic acids.

Accurate analytical figures could not be obtained, presumably because of the hygroscopic properties of the product.

Lactone (XXV) from the Amino Acid (XXIV)

A mixture of 1.36 g. of the preceding amorphous amino acid and 160 mg. of trioxymethylene in 6 ml. of trifluoroacetic acid was allowed to stand at room temperature for 6 days. The solution was taken down to dryness *in vacuo* and the residue treated with cold aqueous sodium carbonate and extracted with ether. The ether extract was washed with several portions of aqueous sodium carbonate, dried, and evaporated to yield an oil which crystallized from ether as colorless needles, m.p. 95–97° (yield: 310 mg.). Recrystallization from acetone–ether raised the m.p. to 97.5–98.5°. Calc. for $C_{16}H_{23}O_3N$: C, 67.89; H, 8.73; N, 5.28; mol. wt. 265. Found: C, 68.00; H, 8.34; N, 5.25; mol. wt. 220 (Rast).

From the combined sodium carbonate washings there was recovered 620 mg. of unchanged starting amino acid, the identity of which was ascertained by mixed paper chromatograms.

The crystalline lactone dissolves in warm aqueous alkali but cannot be recovered from its solution. In the infrared region is exhibited a band at 1770 cm^{-1} (CHCl_3). It was transparent in the ultraviolet region.

1,11-Ethylene-1-azaspiro[5,5]undecane-5-(β -hydroxyethyl)-5-ol (XXVI)

To a solution of 100 mg. of lithium aluminum hydride in 2 ml. of tetrahydrofuran was added 50 mg. of the preceding lactone and the mixture was allowed to stand overnight after which time it was decomposed with aqueous sodium hydroxide. The mixture was worked up in the usual way to yield a colorless oil which crystallized from hexane. Two recrystallizations from hexane afforded fine colorless needles, m.p. 78–79°. Calc. for $C_{14}H_{25}O_2N$: C, 70.25; H, 10.52. Found: C, 69.95; H, 10.48. It was insoluble in hot aqueous alkali and showed no absorption in the carbonyl region in the infrared.

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THE PRINS REACTION WITH β,γ -UNSATURATED ACIDS AND AMIDES¹

B. BELLEAU

ABSTRACT

The acid catalyzed condensation of cyclohexenylacetic acid and its corresponding N-methylamide with formaldehyde was investigated. Good yields of the expected δ -lactone (V) or δ -lactam (IX) were obtained when trifluoroacetic acid was used both as catalyst and solvent for the reaction.

In connection with another problem (2), it was of interest to develop a specific method for the synthesis of β,γ -unsaturated- δ -lactones from β,γ -unsaturated acids of the cyclohexane series. On theoretical grounds, the Prins reaction (1) appeared attractive since it can be expected that the carboxyl group of the unsaturated acid would participate in the condensation through the formation of intermediates II and III, thus bringing about favorable proximity of carbonium ion III to the double bond. In this manner, ring closure to the desired lactone should be facilitated. The Prins reaction as applied to a long chain ω -unsaturated acid has been reported recently by Braude and co-workers (4) but there appears to exist no report on the behavior of β,γ -unsaturated acids in this reaction.

In a preliminary experiment, cyclohexeneacetic acid (I) was treated with trioxymethylene in boiling acetic acid as solvent and sulphuric acid as the catalyst to give a 45% yield of a neutral liquid whose properties agreed with structure V. The product was insoluble in cold but soluble in warm aqueous alkali, had the correct saponification equivalent, and exhibited a band in the infrared region at 1750 cm^{-1} which is characteristic of a β,γ -unsaturated- δ -lactone. In an attempt to improve the yield of lactone (V), the reaction was carried out in dioxane as the solvent and again sulphuric acid as the catalyst. Surprisingly, there was obtained also in 45% yield a single crystalline substance which proved to be the isomeric conjugated lactone (VI) on the basis of its typical behavior toward alkali and the following spectral evidence: it exhibited strong absorption in the ultraviolet region at $223\text{ m}\mu$ ($\log \epsilon = 3.95$) and a characteristic band in the infrared region at 1733 cm^{-1} , in agreement with an α,β -unsaturated- δ -lactone structure. It is of practical interest that both lactones can be obtained essentially free from one another by the simple expedient of substituting dioxane for acetic acid or vice versa. The reasons for this are not clear.

In subsequent attempts to improve the yield of lactone (V), it was ultimately found that trifluoroacetic acid can serve both as solvent and catalyst in this reaction and that it appears to be the reagent of choice for our purposes. Indeed, by the simple expedient of mixing equimolar amounts of cyclohexeneacetic acid and trioxymethylene in trifluoroacetic acid at room temperature, the unconjugated lactone (V) was obtained consistently in yields of 75 to 80% of the theoretical. This new technique may prove of value in the general application of the Prins reaction.

In connection with still another problem (2), it was necessary to explore the possibility of applying the Prins reaction to the corresponding β,γ -unsaturated amides with a view to preparing octahydroisoquinolones such as IX. The successful application of the

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Pictet-Spengler synthesis to cyclohexenylethylamine, as reported by Grewe (5), coupled with our recent finding that arylacetamide derivatives can substitute advantageously for phenethylamines in the same reaction (3) raised the question whether cyclohexenylacetamide derivatives can also be of use in the Pictet-Spengler reaction. At this point, with formaldehyde as a reactant, no fundamental mechanistic demarcation can be discerned between the Pictet-Spengler and Prins reactions except perhaps that the former implies participation of a basic nitrogen leading to a Schiff base type of compound

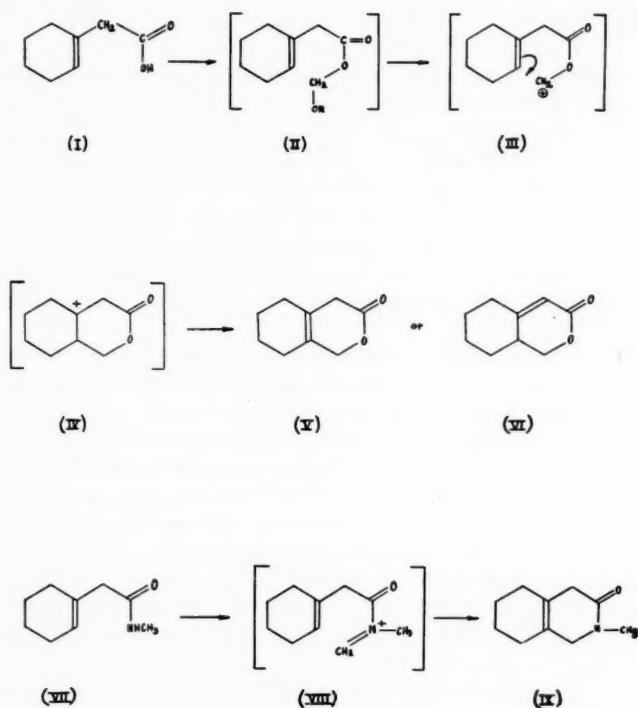


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as an intermediate. For this reason, the term Pictet-Spengler reaction may be more appropriate in the case under discussion. The condensation of N-methyl cyclohexenylacetamide with formaldehyde was therefore investigated and, taking advantage of our experience in the Prins reaction as described above, the amide was reacted with trioxymethylene in hot trifluoroacetic acid. In this manner, there was obtained in 65% yield a colorless liquid whose properties agreed with structure IX. Inertness to warm alcoholic alkali, transparency in the ultraviolet region, and strong absorption in the infrared region at 1655 cm^{-1} served to establish that the reaction followed the anticipated course. It is of practical interest that octahydro-3-isoquinolones appear to be easily accessible by this method and further applications of this finding are described in a separate communication.

EXPERIMENTAL*

2-Hydroxymethyl-1-cyclohexeneacetic Acid Lactone (V)

Method A.—A solution of 16 g. of cyclohexeneacetic acid and 4 g. of trioxymethylene in 50 ml. of acetic acid containing 0.5 ml. of concentrated sulphuric acid was heated under reflux for 5 hours, after which time the mixture was cooled and treated with 2 g. of anhydrous sodium acetate. Distillation *in vacuo* gave 8 g. (46% yield) of colorless liquid, b.p. 145–147° at 8 mm. The product is insoluble in cold aqueous sodium hydroxide but dissolves readily upon warming. It gave a band in the infrared at 1750 cm^{-1} (CS_2). Calc. for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.02; H, 7.95. Found: C, 71.18; H, 7.82.

Method B.—Cyclohexeneacetic acid (14 g.) was mixed at room temperature with a solution of 3.16 g. of trioxymethylene in 40 ml. of trifluoroacetic acid. After it had been left for 40 hours at room temperature, the solution was distilled *in vacuo* to give at 158–160° and 12 mm. 11.5 g. (75% yield) of colorless liquid which proved identical in the I.R. region with the preceding lactone.

2-Hydroxymethyl-cyclohexylideneacetic Acid Lactone (VI)

A mixture of 8 g. of cyclohexeneacetic acid, 2 g. of trioxymethylene, 35 ml. of dioxane, and 0.25 ml. of concentrated sulphuric acid was heated to 95° for 18 hours. The solution was concentrated *in vacuo*, the residue taken up in ether, and the solution washed several times with dilute aqueous sodium bicarbonate. The ethereal phase was dried and evaporated and the residue distilled *in vacuo*; at 150–152° and 7 mm., there was obtained 4 g. (46% yield) of crystalline distillate. It was recrystallized from ether–hexane to give colorless needles, m.p. 59–60°; $\lambda_{\text{max}}^{\text{EtOH}} = 223 \text{ m}\mu$ ($\epsilon = 9000$); absorption maxima in the I.R. at 1733 cm^{-1} and 1700 cm^{-1} (CS_2). The product is soluble in warm aqueous sodium hydroxide but not in the cold. Calc. for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.02; H, 7.95. Found: C, 71.22; H, 8.10.

N-Methyl Cyclohexeneacetamide (VII)

This was prepared in the usual fashion from cyclohexeneacetyl chloride and aqueous methylamine. The product crystallized from hexane as colorless leaflets, m.p. 33–34°. Calc. for $\text{C}_9\text{H}_{16}\text{ON}$: N, 9.14. Found: N, 9.26.

2-Methyl- $\Delta^{9(10)}$ -octahydro-3-isoquinolone (IX)

A mixture of 13 g. of the preceding amide, 2.7 g. of trioxymethylene, and 35 ml. of trifluoroacetic acid was heated on the steam bath for 6 hours, after which time it was distilled *in vacuo*; at 158–160° and 12 mm., there was obtained 10 g. of a colorless liquid. This was further purified by treatment with hot methanolic sodium hydroxide for 3 minutes, followed by extraction with ether and isolation by distillation. If this treatment was omitted, the analytical values for nitrogen were too low. This product gave a band in I.R. at 1655 cm^{-1} (CS_2) as expected for IX and did not consume alcoholic sodium hydroxide after 1 hour at reflux temperature. Calc. for $\text{C}_{10}\text{H}_{16}\text{ON}$: C, 72.68; H, 9.15; N, 8.48. Found: C, 72.51; H, 9.29; N, 8.42.

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*All melting and boiling points are uncorrected. Analyses by Mr. B. Mercier of these laboratories.

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THE LOCATION AND DISTRIBUTION OF SUBSTITUENTS IN A PURIFIED HYDROXYETHYL CELLULOSE¹

H. H. BROWNELL² AND C. B. PURVES

ABSTRACT

A purified hydroxyethylcellulose of molar substitution 1.33 was completely hydrolyzed in acid, and paper chromatography of the neutral hydrolyzate separated glucose, the three possible hydroxyethyl glucoses, the three di(hydroxyethyl) derivatives, and 2,3,6-tri-*O*-hydroxyethyl glucose. These substances were isolated as sirups possibly contaminated with the corresponding hydroxyethoxyethyl and higher homologues, which had nearly the same R_f values in the system used. The chromatographic behavior of each of the seven hydroxyethyl glucoses was established by synthetical methods from methyl 4,6-*O*-benzylidene glucoside, 1,2:5,6-di-*O*-isopropylidene, and 1,2:3,5-di-*O*-methylene glucofuranose. Methyl 2,3-di-*O*-hydroxyethyl-4,6-*O*-benzylidene- β -glucopyranoside, m.p. 98°–100° and 119–121°, and 1,2-mono-*O*-methylene glucofuranose, m.p. 147°, were new substances.

A quantitative examination of the hydrolyzates showed that the condensation between alkali cellulose and ethylene oxide was nearly homogeneous, that the primary hydroxyl groups in the anhydroglucose units reacted fastest, and those in the third positions slowest. The average substituent had a polyoxyethylene chain length of 1.6 units. Three commercial hydroxyethylcelluloses of apparent M.S. about 1.4 contained non-carbohydrate polyethylene glycols.

INTRODUCTION

It has long been known that the condensation of alkali cellulose with ethylene oxide or ethylene chlorohydrin yields the commercially valuable hydroxyethylcelluloses, the literature of which has been reviewed (26). The problem of locating the position of the substituents in these derivatives is unusually complicated, because any particular hydroxyl group in the cellulose might become substituted by a polyethylene oxide chain instead of by the monomeric hydroxyethyl unit, and in consequence the actual degree of substitution in the glucose residues (D.S.) would be less than the observed molar substitution (M.S.). Division of M.S. by D.S. would give the average length of the polyethylene oxide chains. Even if the maximum chain length were only three units, there are 64 different ways in which a single glucose residue in the cellulose derivative could be substituted. Moreover, the customary methods of locating substituents in cellulose ethers proved to be of limited value for the hydroxyethyl derivatives. The tosylation-iodination method of differentiating primary from secondary alcoholic groups was found by Tasker and Purves (26) and by Fournier (11) to be attended by side-reactions, one of which probably involved the elimination of hydroxyethyl groups. Sonnerskog (24) and Cohen and Haas (3) estimated unsubstituted 2,3-glycol groups by oxidation with lead tetraacetate or with periodate, but the occurrence of overoxidation necessitated an extensive correction. It became obvious that a thorough structural study of the hydroxyethylcelluloses required the development of new methods.

Creamer, Brownell, and Purves (5) then observed that crystalline 3-*O*-hydroxyethyl- α -D-glucose gave a single, well-defined spot of R_f 0.180 when chromatographed on paper with butanol saturated with water as the eluant. Although this spot was easily differentiated from that of R_f 0.09 given by glucose, it was practically coincident with that of 3-*O*-hydroxyethoxyethyl glucose, R_f 0.187. Chromatography had to be prolonged for

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many days to separate the last two spots completely. Since the R_f values of the hydroxyethyl, $\text{HOCH}_2\text{CH}_2-$, and the hydroxyethoxyethyl, $\text{HOCH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-$, derivatives did not differ by more than 3 or 4% in the system used, and the difference was probably no greater for higher homologues, it seemed probable that the chromatography of a completely hydrolyzed hydroxyethylcellulose would yield no more than eight spots corresponding to glucose, and to glucose substituted in the 2-, 3-, 6-; 2,3-, 2,6-, 3,6-; and 2,3,6-positions, by polyethylene oxide chains of variable length. The present article describes the identification and estimation of the material in these spots, and discusses the structure of the original hydroxyethylcellulose in the light of the results.

Although the paper chromatographic behavior of authentic ethylene glycol, diethylene glycol, and triethylene glycol could not be detected by the aniline phthalate spray used for reducing sugars, these compounds were readily distinguished from sugars by the distinct brown spots of R_f 0.55, 0.62, and 0.63, respectively, which they gave when an ammoniacal silver spray was employed. When ethylene oxide was bubbled into water (mole ratio 1:13 or only 1:1.1) containing sodium hydroxide, and the resulting mixtures of glycols were chromatographed on paper, the spot of R_f 0.63 was marked and that of R_f 0.55 was faint. Polyethylene glycols therefore formed in preference to ethylene glycol under conditions similar to those used in the preparation of hydroxyethylcelluloses. Weibull and Nycander (28) similarly found that ethylene oxide condensed more rapidly with ethoxyethanol than with ethanol itself. In a search for physically adsorbed polyethylene glycols, hydrolyzates of six commercial hydroxyethylcellulose ethers were chromatographed on paper simultaneously with reference samples of ethylene glycol. Polyethylene glycols, but not ethylene glycol itself, were present in three hydroxyethylcelluloses of specified M.S. about 1.4, but were absent in three lots of M.S. 0.44 to 0.82.

An aqueous solution of one of these commercial products, Cellosize WS-100 with an observed M.S. 1.56, was then poured into a large volume of acetone and the precipitate was reprecipitated in the same way. This treatment gave a product whose M.S. was decreased to 1.33, but which after hydrolysis was chromatographically free of polyethylene glycols. Evaporation of the mother liquors from the precipitations recovered 4.2% of the original sample as a distillable oil with a combined ethylene oxide content of 83.9%—or a value intermediate between those of di- and tri-ethylene glycol. This non-carbohydrate oil contained 12% of the combined ethylene oxide content of the original hydroxyethylcellulose and accounted for 0.18 units in its apparent M.S. of 1.56.

Although Davis (7) described hydroxyethylcelluloses of M.S. as high as 6, the analytical method he used was unreliable. Morgan (15), however, condensed ethylene oxide and alkali cellulose in a mole ratio of 10:1 to prepare a sample of M.S. 4.1, determined after purification by a series of precipitations and leachings followed by dialysis. In this case the M.S. was found by Morgan's own reliable method, but the efficacy of the purification in removing adsorbed polyethylene glycols had to be assumed. Since the amount of the latter retained by such a highly substituted product might be considerable, a hydroxyethylcellulose was prepared by condensing alkali cellulose with ethylene oxide in a molar ratio of 25:1, and was unequivocally freed of polyethylene glycols by precipitations from aqueous acetone. The fact that the M.S. was 6.9 confirmed earlier claims that values greater than 3.0 could be attained, and that true polyethylene oxide substituents actually existed in hydroxyethylcelluloses.

A sample of the purified hydroxyethylcellulose of M.S. 1.33 was then completely hydrolyzed in acid. The neutral hydrolyzate, when chromatographed on paper for a prolonged period, yielded eight distinct spots shown in Fig. 1 and numbered according to increasing R_f values. Since Dolgoplov, Melnikov, and Nametkin (9) found that 1% of concentrated sulphuric acid promoted an equilibrium between the monoalkyl ethers of ethylene, diethylene, and polyethylene glycols, it was possible that a similar migration or cleavage had occurred during the above hydrolysis. This possibility was discounted, because careful examination of the chromatograms revealed no traces of spots attributable

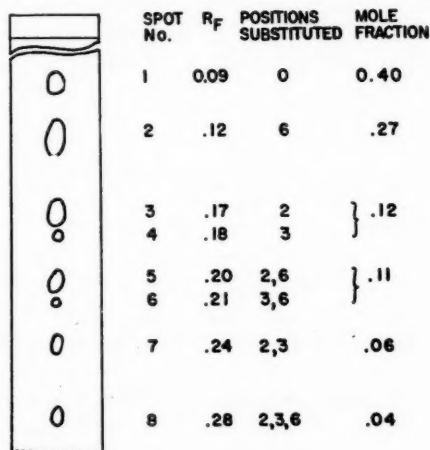
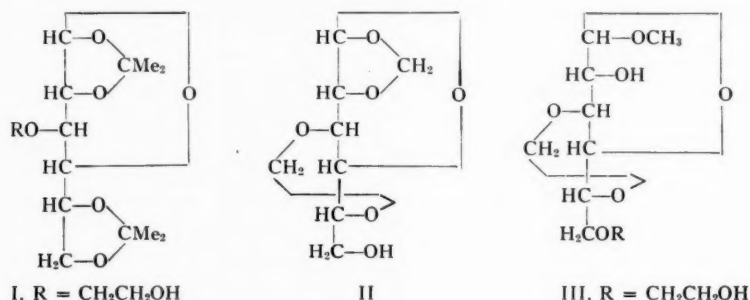


FIG. 1. Paper chromatogram of hydroxyethyl glucose mixture from hydrolyzed hydroxyethylcellulose, M.S. 1.33, D.S. 0.85. Developer: Butanol-1 saturated with water. Spray: Aniline phthalate.

to the polyethylene glycol series. Since crystalline 3-*O*-hydroxyethyl glucose was still chromatographically pure after subjection to the same conditions of hydrolysis, a migration of hydroxyethyl units within the glucose structure was also improbable.

The sugar, or series of sugars, causing each spot was then identified. Spot 1 was ascribed to glucose, which had the same R_f value. In confirmation, fermentation of the hydrolyzate with yeast removed this spot, and only this spot, from the subsequent chromatogram. Synthetic 3-*O*-hydroxyethyl glucose, when chromatographed simultaneously with the hydroxyethylcellulose hydrolyzate, had an R_f value identical with that of spot 4. Information about the chromatographic behavior of glucose substituted in the 2- and 2,3-positions was obtained by condensing methyl 4,6-*O*-benzylidene- α - or - β -D-glucopyranoside with ethylene oxide. When a suitable excess of the reagent was used, methyl 2,3-di-*O*-hydroxyethyl-4,6-*O*-benzylidene- β -glucoside was isolated as a new, crystalline compound, which when hydrolyzed yielded 2,3-di-*O*-hydroxyethyl glucose as a chromatographically pure sirup. This hydrolyzate, when chromatographed, gave a single spot identical in R_f value to spot 7. When the benzylidene glucoside was condensed with a lesser amount of ethylene oxide, and the uncrystallized product was hydrolyzed, the resulting mixture of hydroxyethyl glucoses gave a chromatogram with only four spots, one for glucose, two for the known 2,3- and 3-derivatives, and a fourth which was ascribed with confidence to 2-*O*-hydroxyethyl glucose. This substance had the same R_f value as spot 3 in Fig. 1.

In order to prepare a known mixture containing 3,6-di-*O*-hydroxyethyl-D-glucose, 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylidene glucose (I) was partially hydrolyzed to a mixture containing much of the 1,2-mono-*O*-isopropylidene derivative. Condensation of the mixture with ethylene oxide, followed by hydrolysis of the remaining 1,2-*O*-isopropylidene group, gave a mixture containing glucose with hydroxyethyl substituents only in the 3-, 3,6-, 3,5-, and 3,5,6-positions. The corresponding chromatogram had four spots,



of which two failed to coincide with any in the chromatogram of the hydrolyzed hydroxyethylcellulose (Fig. 1). These spots were ascribed to the 3,5- and 3,5,6-derivatives. One of the other spots was that of the known 3-derivative, and by elimination the fourth spot was that of 3,6-di-*O*-hydroxyethyl glucose. This spot coincided with spot 6 in Fig. 1.

Five years ago, Hough, Jones, and Magson (13) condensed glucose with formaldehyde and isolated a new, non-reducing dimethylene glucose (II) as a crystalline 6-acetate. After this acetyl group had been saponified and replaced with a hydroxyethyl unit, hydrolysis yielded an uncrystallized sample of 6-*O*-hydroxyethyl glucose. Chromatographic comparison with Fig. 1 then indicated that spot 2 was caused by glucose substituted in the sixth position. A partial hydrolysis of the dimethylene glucose (II) then gave two new monomethylene derivatives, one a reducing sirup and the other a crystalline compound. Since the latter was non-reducing, one point of attachment of the methylene group was at the 1-position of the glucose. This compound and also crystalline 1,2-*O*-isopropylidene glucose were then condensed with ethylene oxide in parallel experiments, and after hydrolysis the two products yielded chromatograms with identical series of spots. The methylene, like the isopropylidene, substituent therefore occupied the 1,2-positions in glucose, which in both cases had a furane or 1,4-ring structure. This ring structure was confirmed by the observation that the monomethylene derivative yielded 1 mole of formaldehyde when oxidized with periodate. The parent substance (II) was therefore 1,2;3,5-di-*O*-methylene glucose, since the sixth position was known to be free, and the uncrystallized, reducing monomethylene glucose was the 3,5-derivative. This simple proof of the structure of the dimethylene glucose (II) supplemented the more rigorous ones given by Schmidt, Distelmaier, and Reinhard (20) and by Shyluk, Honeyman, and Timell (22). Shyluk and Timell (23) also synthesized the 2-, 3-, and 6-*O*-hydroxyethyl glucoses, as well as 3-*O*-hydroxyethoxyethyl glucose, by reducing the corresponding carboxymethyl ethers with lithium aluminum hydride, and noted their chromatographic behavior.

The 6-*O*-hydroxyethyl derivative of II was then partly hydrolyzed to the two analogous monomethylene derivatives, and a sample of the reducing one, 6-*O*-hydroxyethyl-3,5-di-*O*-methylene glucofuranose, was isolated as a sirup from a series of paper chromatograms. In accord with its furanose structure, this sugar was easily converted to a mixture of methyl α - and β -glucosides (III) by methanol and hydrogen chloride. Condensation of this glucoside with ethylene oxide caused the substitution of the hydroxyl group in the second position, and hydrolysis of the methyl and methylene groups yielded 2,6-di-*O*-hydroxyethyl glucose as a sirup whose R_f value was identical to that of the sugar producing spot 5 in Fig. 1. Conversion of this 2,6-derivative to its methyl glucopyranoside, condensation of the latter with ethylene oxide, and subsequent hydrolysis of the methyl group gave a mixture which produced a chromatogram with three spots. One of these spots was that of unchanged 2,6-di-*O*-hydroxyethyl glucose, and another was probably caused by the 2,4,6-derivative, since it did not appear in the chromatogram of hydrolyzed hydroxyethylcellulose (Fig. 1). The third spot coincided exactly to spot 8 in Fig. 1, and was therefore ascribed to 2,3,6-tri-*O*-hydroxyethyl glucose.

All eight spots in Fig. 1 were thus individually identified as one or other of the eight sugars or series of sugars theoretically to be expected from the hydrolysis of a hydroxyethylcellulose. Although the identifications were based almost entirely on paper chromatograms and were therefore not conclusively proved, they were complete and self-consistent. Spots 4 and 6 were difficult to resolve from spots 3 and 5, respectively, and at one time the possibility was considered that the former pair were simply the hydroxyethoxyethyl or higher derivatives of the latter. This possibility was remote because the relative intensities of the spots from the hydrolyzates of hydroxyethylcelluloses of M.S. 1.33 and 0.44 were approximately the same, in spite of the fact that the latter sample should have contained much less hydroxyethoxyethyl substitution than the former. When a sample of crude 6-*O*-hydroxyethyl glucose prepared with a large excess of ethylene oxide was chromatographed on paper for 10 days, the original single spot separated into two spots very close together, one of which could be ascribed to the hydroxyethoxyethyl glucose by analogy with the similar behavior of the 3-*O*-hydroxyethyl derivatives (5, 23). In a few of many attempts made with the hydrolyzed hydroxyethylcellulose of M.S. 1.33, an incomplete resolution of the spot ascribed to 6-*O*-hydroxyethyl glucose (No. 2, Fig. 1) was obtained, and the presence of two or more ethylene oxide units in this position of the hydroxyethylcellulose was considered probable.

The hydrolyzate of the hydroxyethylcellulose was then chromatographed on a larger scale, so that the material in the various spots could be recovered quantitatively. The two weakest spots in Fig. 1, Nos. 4 and 6, which were later estimated to represent less than 4% of the sugars—and which were difficult to resolve—were included with the adjacent spots, Nos. 3 and 5, respectively. Reducing sugars in each extract were then determined by oxidation with alkaline hypoiodite, since this method was found to be very satisfactory for the estimation of pure 3-*O*-hydroxyethyl glucose. Column 4 of Fig. 1 gives the results as mole fractions of the hydroxyethylcellulose substituted in the positions indicated in Column 3.

The degree of substitution (D.S.) of this hydroxyethylcellulose was calculated to be 0.85, and the average number of ethylene oxide units in a substituent group was $1.33/0.85$, or about 1.6. Reese, Siu, and Levinson (18) observed that the low resistance of a hydroxyethylcellulose of M.S. 1.47 to biological degradation suggested a D.S. of only 0.8 to 0.9, and concluded that their sample contained polyoxyethylene substituents averaging

1.6 to 1.8 units in length. The average number of primary alcohol groups in the hydroxyethylcellulose was obviously unity plus the D.S. in the 2-, 3-, 2,6-, 3,6-, and twice the D.S. in the 2,3- and 2,3,6-positions (Fig. 1). This number, 1.43 per anhydroglucose unit, lay between the values of 1.22 and 1.46 found by the tosylation-iodination method for hydroxyethylcelluloses of M.S. 0.44 (26) and 1.50 (3) respectively. The number of unsubstituted 2,3-glycol units in the present sample was 0.67, whereas Cohen and Haas (3) found by the periodate method that only 0.5 mole was present in their sample of M.S. 1.50. In this case the agreement was poor, presumably because overoxidation occurred in the latter estimation. The data of Fig. 1 also showed that the substitution in the sixth or primary alcohol positions of the hydroxyethylcellulose was 0.42 mole per anhydroglucose unit, or was one-half of the total D.S. of 0.85. The condensation of ethylene oxide therefore proceeded most rapidly with the primary alcohol units in the alkali cellulose; condensation with the unit in the second position was substantial, and was least with that in position three.

Spurlin (25) and Timell (27) calculated that if substituents in cellulose were distributed between the second, third, and sixth positions, equations of the form

$$x_2 = S_2 + S_{2,3} + S_{2,6} + S_{2,3,6}$$

were valid. If the distribution was according to the laws of chance, then

$$S_2 = x_2(1-x_3)(1-x_6).$$

There were similar equations for S_3 to $S_{2,3,6}$. In these equations, x_2 , x_3 , and x_6 were the over-all mole fractions of the anhydroglucose units substituted in the positions indicated by the subscript, while S_2 , $S_{2,3}$, etc. gave the fractions substituted *only* as indicated. The failure to estimate S_3 and $S_{3,6}$ independently of S_2 and $S_{2,6}$ (Fig. 1) made it necessary to assume that the former substitutions were zero or had some small value like 0.02 mole. The first equations were then used to calculate x_2 , x_3 , and x_6 , and the second group could then be solved for S_0 to $S_{2,3,6}$. Although none of the assumptions made gave close agreement between the calculated S values and those observed (Fig. 1), the great discrepancies observed by Timell (27) for methylcelluloses prepared in a heterogeneous system were absent. The reaction between alkali cellulose and ethylene oxide therefore appeared to be more homogeneous than the corresponding methylation. Cohen and Haas (3) reached the same conclusion for other reasons.

Four months ago, Croon and Lindberg (6) published an interesting article on the location of the substituents in a hydroxyethylcellulose of M.S. 0.60–0.55. The hydrolyzate was separated into 15 fractions (including hydroxyethoxyethyl and higher homologues) by elution from a carbon–Celite column, and glucose, the 2-, 3-, and 6-*O*-hydroxyethyl glucoses, and six uncrystallized disubstituted ethers were isolated in a pure or nearly pure form. These products were characterized by their relative mobilities in paper chromatography before and after oxidation with periodate according to Lemieux and Bauer (14), and also by their relative mobilities during electrophoresis in a borate buffer (10). These identifications, like those in the present article, depended for the most part on indirect methods, but the agreement in the results of the two independent researches tended to confirm the validity of both. Croon and Lindberg's more detailed statistical analysis of the distribution of substituents also suggested that all the anhydroglucose units in alkali cellulose were equally accessible to ethylene oxide, and that hydroxy groups in C_6 , C_2 , C_3 , and hydroxyethyl positions condensed at rates proportional to 10:3:1:20.

EXPERIMENTAL

Materials and Methods

Unless otherwise mentioned, the alkali used in condensations with ethylene oxide was aqueous 5% sodium hydroxide at 70–75°. Combined ethylene oxide content was estimated by Morgan's modified Zeisel method (15). All chromatograms were prepared on Whatman No. 1 or No. 4 paper by the descending flow technique (1) with *n*-butanol saturated with water. An aniline phthalate spray (17) was used to locate reducing sugars, and ammoniacal silver nitrate (16) for non-reducing substances. With the exceptions noted below, the chromatographic behavior of the various preparations was discussed in the Introduction. Analyses for substituent groups were corrected for ash.

Polyethylene glycol, sample A, was prepared by passing 5.5 g. (0.125 mole) of commercial ethylene oxide gas during 45 minutes through a fritted glass Filterstick into 30 ml. (0.04 mole) of alkali. After being kept for an additional 75 minutes at 70°, the solution was passed through a column of Amberlite IR-120 to remove the base, and evaporation of the neutral effluent yielded 6.31 g. of a colorless oil. To prepare sample B, a 50 ml. flask was loosely packed with glass wool wet with 3.2 ml. (0.18 mole) of water containing 1.8 g. of sodium hydroxide. After being evacuated, 7.1 g. (0.16 mole) of ethylene oxide gas was gradually introduced. The product was extracted from the glass wool with 70 ml. of water and was isolated as in the previous case.

Examination and Preparation of Hydroxyethylcelluloses

One-gram samples of six commercial hydroxyethylcelluloses were separately heated with 25 ml. volumes of 2% hydrochloric acid for 14 hours at 100° in sealed tubes filled with nitrogen. Four samples, of specified M.S. 0.8 or more, dissolved almost completely, but two, of M.S. 0.39 and 0.44, to the extent of only 80%. Each hydrolyzate was centrifuged, deacidified by passage through Amberlite IR-4B resin, and evaporated to 50 ml. Paper chromatograms were then prepared simultaneously from 0.007 ml. aliquots of these solutions, and from 0.0003 ml. reference samples of pure ethylene glycol. When sprayed with ammoniacal silver nitrate, the hydrolyzates from three hydroxyethylcelluloses of apparent M.S. 1.4, —, 1.44 gave spots with the R_f value of polyethylene glycol; one sample of M.S. 0.82, which was swollen in water, and two water-insoluble samples of M.S. 0.44 and 0.39 appeared to contain none of these glycols, even when 0.02 ml. aliquots were chromatographed.

One sample, Cellosize WS-100 of specified M.S. 1.44 and containing 6.2% of moisture, was analyzed. Found (oven-dry basis): ash, 2.88; OCH_2CH_2 , 29.7, 29.8, 29.7%, corresponding to the apparent M.S. 1.56. A solution of 9.6 g. in 86 ml. of water was poured slowly, with stirring, into 860 ml. of acetone and the precipitate was recovered on the centrifuge. Evaporation of the mother liquors gave 0.37 g. (4.2%) of a yellow oil. Found: OCH_2CH_2 , 83.9%. Calc. for $\text{H}(\text{—OCH}_2\text{CH}_2)_2\text{OH}$: 83.05; for $\text{H}(\text{—OCH}_2\text{CH}_2)_3\text{OH}$: 88.0%. The oil distilled at 0.2 mm. pressure from a bath at 200° and a chromatogram prepared from 0.0005 ml. showed only one spot with the R_f value of polyethylene glycols. A second precipitation of the hydroxyethylcellulose yielded only 0.05 g. of these glycols. After this second purification, the air-dry product was dissolved in water and recovered by evaporation to free it from traces of acetone. Found (oven-dry basis): ash, 2.50; $\text{—OCH}_2\text{CH}_2$, 26.6, 26.5%, corresponding to M.S. 1.33. This sample, which was chromatographically free of polyethylene glycols, was used in the later work (Fig. 1).

To prepare a highly substituted hydroxyethylcellulose, 5 g. of linters was steeped in

30% sodium hydroxide and the mass was pressed to a weight of 14.6 g. Ethylene oxide was passed into a partially evacuated flask containing this alkali cellulose and cooled externally in water. After 5 hours, when the gain in weight was 34.2 g., the contents of the flask were dissolved in 700 ml. of water, freed of base, and concentrated to 300 ml. The solution was precipitated into 6 l. of acetone. After two similar precipitations the product was chromatographically free of polyethylene glycols. Found (oven-dry basis): ash, 0.24; $-\text{OCH}_2\text{CH}_2$, 65.6, 64.9%, corresponding to M.S. 6.9. A large part of the ethylene oxide had yielded non-carbohydrate products, of which 28.9 g. was recovered from the mother liquors as a crude oil. The hydroxyethylcellulose could also be purified by dialysis against water for 14 days.

Methyl 2,3-Di-O-hydroxyethyl-4,6-O-benzylidene- β -D-glucopyranoside

Ethylene oxide gas, 71 g. (1.62 mole), was passed into a slurry of pure methyl 4,6-O-benzylidene- β -glucoside, 5 g. (0.018 mole), in 25 ml. of alkali during 3.5 hours, the mixture being maintained at 90–95°. The gain in weight was 31.7 g. The resulting solution was neutralized with hydrochloric acid and extracted with five 65-ml. volumes of ethyl acetate; these extracts were combined, washed with small volumes of water, and evaporated to an oil which crystallized on standing. Yield: 6.85 g. or 104%. Two recrystallizations from 50 ml. of water, or one from water and one from isopropyl ether, left about 25% of the product with a melting point of 98–100°. The substance, however, recrystallized in the melting point tube and remelted at 119–121°. The higher melting form, which had the same composition as the other, separated from an aqueous solution which had been boiled for 10 minutes. Found: C, 58.5, 58.2; H, 7.2, 6.9; alkoxyl as $-\text{OCH}_2\text{CH}_2$, 34.2%. Calc. for $\text{C}_{18}\text{H}_{26}\text{O}_8$: C, 58.4; H, 7.1; alkoxyl as $-\text{OCH}_2\text{CH}_2$, 35.7%.

2,3-Di-O-hydroxyethyl Glucose

A solution of 0.05 g. of the above benzylidene methyl glucoside in 5 ml. of 3% hydrochloric acid was kept at 100° for 3.5 hours. The hydrolyzate was extracted with three 1-ml. volumes of chloroform to remove benzaldehyde, was deionized, and was evaporated to a colorless sirup. A paper chromatogram of this sirup revealed only one spot, which was attributed to 2,3-di-O-hydroxyethyl glucose.

2- and 3-O-Hydroxyethyl-D-glucose

(a) Ethylene oxide gas, 2.2 g. (50 mM.), was bubbled through a glass capillary into a solution of 0.25 g. of pure methyl- α -4,6-O-benzylidene glucoside (0.89 mM.) in 6.3 ml. of alkali. One hour after the addition was complete, the solution was extracted with three 1.5-ml. volumes of chloroform; the combined extracts were washed with a little water, and evaporation of the chloroform left 0.27 g. of sirup. When hydrolyzed as just described for the 2,3-di-O-hydroxyethyl derivative, and chromatographed on paper, this sirup gave the spots for glucose, 3-O-hydroxyethyl glucose, and spot 3 in Fig. 1, which was assigned to 2-O-hydroxyethyl glucose.

(b) Preparation (a) was repeated with five times as much ethylene oxide, the time of addition being 1 hour. When the product, 0.37 g., was hydrolyzed and chromatographed on paper, only the spots for the known 3-O-hydroxyethyl and the 2,3-di-O-hydroxyethyl glucoses appeared, together with the one attributed to the 2-derivative.

6-O-Hydroxyethyl-D-glucose

(a) A solution of 1,2;3,5-di-O-methylene-D-glucufuranose 6-acetate (13), 2.5 g. (0.01 mole), was saponified in 15 ml. of alkali kept for 70° for 15 minutes. Then 4.4 g. (0.1 mole)

of ethylene oxide gas was bubbled into the solution during 1 hour at 70°, and 2 hours later the solution was extracted with six 7-ml. volumes of chloroform. The combined extracts were washed with small volumes of water and were evaporated to an oil, which was dried *in vacuo* over phosphorus pentoxide for 10 days. Yield, 2.59 g. or 103%. This oil was hydrolyzed by boiling for 12 hours with 20 parts of 2% hydrochloric acid, and after the solution had been deionized and evaporated crude 6-*O*-hydroxyethyl glucose remained as an uncrystallized sirup. An aliquot, when chromatographed, gave the spot for glucose and spot 2 of Fig. 1.

(b) Preparation (a) was repeated with three times as much ethylene oxide added during 3 hours. After the product had been hydrolyzed, its chromatogram was developed for 5 days on a 75 cm. length of Whatman No. 1 paper. No spot for glucose appeared, but the spot for the 6-*O*-hydroxyethyl derivative was resolved into two spots differing in R_f value by 8%.

3,6-Di-*O*-hydroxyethyl Glucose

Six 0.1-g. samples of 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylidene-D-glucofuranose (I) (5) were boiled in 1 ml. volumes of dry ethyl acetate containing 1% of concentrated nitric acid for 0.5, 2, 8, 12, 20, and 60 minutes. Each solution was neutralized with 0.025 g. of sodium bicarbonate plus 1 drop of water, and was evaporated to dryness. The partly hydrolyzed products were extracted from the residues with acetone, which was later evaporated. Paper chromatograms of the last two products, developed for 12 hours, showed only spots for the original di-isopropylidene derivative (R_f 0.84), faint spots for 3-*O*-hydroxyethyl glucose (R_f 0.18), and a third at R_f 0.71. The inference that the latter spot pertained to 3-*O*-hydroxyethyl-1,2-*O*-isopropylidene glucofuranose was supported by the observation that the R_f value in similar chromatograms of 1,2-*O*-isopropylidene glucofuranose (4) lay between those of glucose and the di-isopropylidene derivative. The chromatograms of the first four partial hydrolyzates revealed increasing amounts of 3-*O*-hydroxyethyl-1,2-isopropylidene glucofuranose, but no hydroxyethyl glucose.

Ethylene oxide gas, 0.1 g., was passed into a solution of half of the neutral product from sample 4 in 0.5 ml. of alkali. After a total time of 1.55 hours, the mixture was extracted with chloroform, and the aqueous residue was saturated with carbon dioxide and evaporated to dryness. The salts were extracted with acetone, which removed the more highly substituted sugars. Evaporation of the acetone solution gave an oil, which was redissolved in 1 ml. of 1% hydrochloric acid and heated at 100° for 3 hours. The resulting hydrolyzate was neutralized with silver carbonate, filtered, saturated with hydrogen sulphide, refiltered, and evaporated to 0.20 ml. Aliquots (0.004 ml., 0.016 ml.) of this solution were chromatographed for 5 days on a 75 cm. strip of Whatman No. 4 paper. One spot was that of 3-*O*-hydroxyethyl glucose; two more, which lay between spots 6 and 7, and 7 and 8 (Fig. 1), were attributed to 3,5-di- and 3,5,6-tri-*O*-hydroxyethyl glucose. The remaining spot was by elimination that of the 3,6-derivative.

The experiment was repeated with the other half of partial hydrolyzate 4 and three times as much ethylene oxide. No additional spots appeared on the chromatogram of the product.

1,2-*O*-Methylene-D-glucofuranose

A solution of 10 g. of 1,2;3,5-di-*O*-methylene glucofuranose 6-acetate in 300 ml. of dry methanol was quantitatively deacetylated at 6° by addition of 1 ml. of 1 *N* barium

methylate in methanol. After isolation 2 days later as a dry sirup, 13 g. of the dimethylene glucose (II) resulting from two runs was heated in 175 ml. of 2% hydrochloric acid at 100° for 1 hour. The solution was deionized, concentrated to 42 ml., and extracted with eight 70-ml. volumes of ethyl acetate to remove unchanged dimethylene glucose, as shown by the disappearance from chromatograms of the spot of R_f 0.65 pertaining to this substance. Fermentation of the aqueous residue then removed glucose, and the liquor was filtered and evaporated to a sirup, which was taken up in ethanol. Filtration and evaporation of this solution yielded 1.95 g. of a sirup which when chromatographed gave only the two spots of R_f 0.32 and R_f 0.46 for 3,5- and 1,2-mono-*O*-methylene glucose, respectively. After this sirup had partly crystallized, it was diluted with 4 ml. of ethanol and the crystals, 0.24 g., were recovered. One recrystallization from 1.5 ml. of ethanol gave pure 1,2-*O*-methylene-D-glucofuranose melting at 146–146.6°. Found: C, 43.8, 43.7; H, 6.1, 6.3%. Calc. for $C_7H_{12}O_6$: C, 43.8; H, 6.3%.

The substance was not reduced by the Shaffer-Somogyi (21) alkaline copper reagent, and oxidation with sodium metaperiodate according to Bourne, Bruce, and Wiggins (2) gave no detectable amount of formic acid within 2.5 hours. A periodate oxidation by the method of Reeves (19), however, yielded 1.025 moles per mole of formaldehyde. Samples of 1,2-*O*-methylene and 1,2-*O*-isopropylidene glucofuranose were condensed with 10 molar equivalents of ethylene oxide in parallel experiments; the products were hydrolyzed and after deionization the two hydrolyzates gave identical chromatograms containing four spots when developed for 5 days on Whatman No. 4 paper.

2,6-Di-O-hydroxyethyl-D-glucose

A chloroform solution containing 6-*O*-hydroxyethyl-1,2,3,5-di-*O*-methylene glucofuranose, contaminated with unchanged dimethylene glucose, was prepared with a 50-fold molar amount of ethylene oxide in the way already described. This product was distilled *in vacuo* without a column, 0.66 g. of forerun and 0.05 g. of still residue being discarded. Partial hydrolysis of the main fraction, 3.5 g., with 25 ml. of 4% hydrochloric acid at 100° for 75 minutes, was followed by deionization of the hydrolyzate, evaporation to 18 ml., and extraction of the liquor with six 10-ml. volumes of chloroform. These extracts contained the dimethylene glucofuranose and its 6-*O*-hydroxyethyl derivative, both of which appeared to have the same R_f value of 0.65. The chromatogram of the aqueous residue gave the four spots characteristic of partial hydrolyzates of the unsubstituted dimethylene glucose (R_f 0.09, 0.32, 0.46, and 0.65), also the one of R_f 0.12 for 6-*O*-hydroxyethyl glucose, and two new ones of R_f 0.38 and 0.55 which were attributed to the 6-hydroxyethyl analogues of 3,5-*O*-methylene and 1,2-*O*-methylene glucofuranose, respectively.

More of the aqueous residue, 0.65 ml., was spotted in 52 aliquots on sheets of Whatman No. 1 filter paper which had been washed with ethanol, and after development for 30 hours the sections containing the substance of R_f 0.38 were cut out and extracted with ethanol. These extracts yielded 38 mg. of a dry, colorless reducing sirup, which was accepted as 6-*O*-hydroxyethyl-3,5-*O*-methylene glucofuranose. Treatment of this sirup with 1% methanolic hydrogen chloride for 45 minutes at room temperature, neutralization with silver carbonate, and evaporation gave the corresponding methyl glucofuranoside (III) as 38 mg. of a non-reducing oil. A 20-fold molar excess, 0.13 g., of ethylene oxide was passed at 70° into a solution of this oil in alkali, and after 1.6 hours the mixture was deionized and evaporated. Hydrolysis of the residual oil by 5 ml. of

2% hydrochloric acid at 100° for 10 hours was carried out in a sealed tube filled with nitrogen. The hydrolyzate, when deionized and evaporated, yielded 45 mg. of a sirup whose chromatogram contained only a single spot which coincided with spot 5 of Fig. 1 and which was attributed to 2,6-di-*O*-hydroxyethyl glucose and its homologues. Non-carbohydrate polyethylene glycols probably contaminated the product.

2,3,6-Tri-O-hydroxyethyl Glucose

The crude 2,6-dihydroxyethyl derivative, 45 mg., was converted to the methyl glucopyranosides by heating for 7 hours at 65° in a sealed tube with 1% methanolic hydrogen chloride. After neutralization with silver carbonate, the liquor yielded a non-reducing oil, which was dissolved in 0.5 ml. of alkali and treated with 0.09 g. of ethylene oxide gas at 73° for 1.5 hours. After recovery by deionization and evaporation, the oil was hydrolyzed in 2 ml. of boiling 2% hydrochloric acid for 3 hours, and the resulting neutral sirup was isolated. The sugars were separated from relatively large amounts of associated polyethylene glycols by spotting some of the sirup on a series of paper chromatograms. After these chromatograms had been developed, the proper sections of the paper were extracted with water by the method of Dent (8), and the extracts evaporated to 0.07 ml. under a jet of nitrogen. When rechromatographed, the sugars gave three spots, one in the position for 2,6-di-*O*-hydroxyethyl glucose, one of *R_f* value between spots 7 and 8 of Fig. 1, and presumably the 2,4,6-derivative, and one coinciding with spot 8, which was accepted as that of the 2,3,6-derivative. The material responsible for spot 8 in the hydrolyzate of the hydroxyethylcellulose was recovered and when rechromatographed still had the same *R_f* value.

Quantitative Determination of Sugars

Exactly 1 g. of the purified hydroxyethylcellulose was hydrolyzed in 50 ml. of 4% hydrochloric acid for 14 hours near 100°, and the hydrolyzate was passed through a column made from 43 ml. of Amberlite IR-4B resin. The neutral effluent, plus 250 ml. of washings from the column, was evaporated under reduced pressure to 5.0 ml., and a series of accurately measured aliquots, each 0.00650 ml., was chromatographed for 2.5 days on Whatman No. 4 paper which had been washed with water. After the sugars were located, they were extracted with water using Dent's technique (8). Spots 3 and 4 (Fig. 1) were extracted together, and so also were spots 5 and 6. In order to obtain consistent blanks, 0.045 ml. of water was used for each square centimeter in the section of paper extracted. The aqueous extracts were not concentrated prior to the determination of their reducing sugar content, because concentration reduced the blank values erratically. The determinations were by stoichiometric oxidation with alkaline hypiodite as described by Hirst, Hough, and Jones (12) and accounted for 93% of the original purified hydroxyethylcellulose.

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THE KINETICS OF ADSORPTION OF *n*-HEPTANE ON CARBON BLACK AT LOW PRESSURES¹

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ABSTRACT

The rates of adsorption at constant pressure of *n*-heptane on 'Spheron 6' carbon black have been measured between 0° and 30° C. in the pressure range 0.005–0.120 mm., using a sensitive quartz spiral technique. From the results the diffusion coefficient has been calculated both as a function of temperature and as a function of surface concentration, and the activation energy for diffusion calculated as a function of surface concentration. The heat of adsorption, calculated as a function of surface concentration from isotherms measured under the above conditions, is the same as the activation energy. Accordingly, a model is proposed in which the heptane molecules diffuse into the powder mass by a series of jumps across the interparticle space. The distribution of heptane within the carbon bed at various times during adsorption has been calculated.

INTRODUCTION

The attainment of adsorption equilibrium with *n*-heptane at room temperature and low pressures has been found to be a slow process on non-porous solids such as graphite (27, 28), molybdenum sulphide (1), and powdered metals (18). Since van der Waals' adsorption per se is invariably instantaneous (7), the delay in reaching equilibrium must be attributed to some slow transport phenomenon. The present study was undertaken in order to determine the mechanism whereby heptane molecules are transferred from the gas phase into the interior of the powder mass.

There exists a comprehensive literature on the diffusion of gases in porous adsorbents (2, 19), but non-porous impermeable powders appear to have received less attention although they offer the considerable advantage that C_0 , the adsorbate concentration on the outer surface of the mass, can readily be evaluated since it is equal to the concentration of adsorbate on the entire adsorbing surface at equilibrium. This parameter is important in the elucidation of the diffusion kinetics. In much of the work reported for porous adsorbents, the value of C_0 could only be estimated (or maintained constant) by approximate methods (14).

The non-porous carbon black designated 'Spheron 6' was deemed the most suitable adsorbent for the present work. It has a specific surface area large enough to permit adsorption measurements to be carried out at constant pressure using a quartz spiral technique, and its crystallographic and adsorptive properties have been extensively examined (6, 5, 17).

EXPERIMENTAL

Materials

A sample of 'devolatilized Spheron 6' was obtained from Godfrey L. Cabot, Inc. through the kindness of Dr. W. D. Schaeffer. Its specific surface area was found to be 131 m.²/g. by the B.E.T. low temperature nitrogen adsorption method (8).

Research grade *n*-heptane (99.9 mole %) was supplied by the National Bureau of Standards.

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Apparatus

Approximately 75 mg. of Spheron 6 was accurately weighed into a small aluminum foil bucket which was suspended from a quartz spiral (maximum load 0.1 g., sensitivity 723.7 cm./g.) supplied by the Houston Technical Laboratories. The bed of carbon was cylindrical in shape, 8 mm. in diameter and 5 mm. deep. The whole assembly was housed in a cylindrical glass envelope, 40 mm. in diameter, connected to the heptane reservoir and vacuum pumps.

The pressure of heptane vapor in the system during an experiment could conveniently be kept constant by the use of a two-phase system, as shown diagrammatically in Fig. 1.

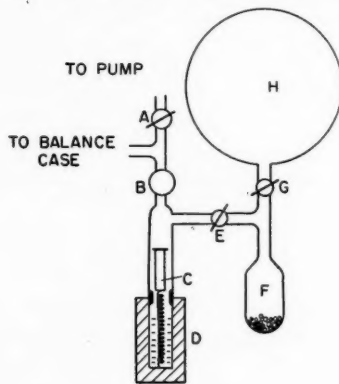


FIG. 1. The heptane reservoir.

The 20 cm.³ sample was contained in a massive brass cylinder D, fitted with thick copper fins (not shown) to facilitate heat transfer between the heptane and the surrounding thermostat bath. The cylinder was connected, via a Kovar-Pyrex seal, directly to the apparatus. The surface of the liquid was continuously renewed by means of a magnetic stirrer comprising an iron slug C soldered to a steel spring. A coil surrounding C was connected, through an appropriate timing device, to a d-c. supply. The trap F containing sodium chips was used for storing the heptane sample when not in use and for bulb-to-bulb distillations. The heptane system could be isolated from the rest of the apparatus by closing a metal diaphragm valve B, supplied by Hoke, Inc. The bulb H was equal in volume to the balance case plus the connecting tubing as far as A and B (Fig. 1); its function will be explained later. Dow-Corning silicone grease proved satisfactory as a stopcock lubricant.

The heptane thermostat consisted essentially of a Dewar flask whose annulus enclosed air at atmospheric pressure. It was filled with acetone and supported inside a larger Dewar flask containing liquid air. The inner bath was fitted with a stirrer, an immersion heater, and a pentane thermometer calibrated at 0° and -78° C. Originally the operation of the immersion heater was controlled by a Cenco bimetallic regulator, but it was later found that closer control could be obtained if a nice balance of the heater voltage and the level of the liquid air in the outer bath were achieved. Using the latter method, the maximum variation never exceeded $\pm 0.1^\circ$, which at the low temperatures employed (-80° to -37° C.) corresponds to a variation in pressure of less than 1%. The choice of vapor pressure data used to calculate the heptane pressures is discussed below.

The adsorption thermostat was contained in an 18 in. deep Dewar vessel equipped with a stirrer and an immersion heater controlled by a chloroform-mercury regulator. To maintain a temperature of 15° C., additional cooling was provided by pumping water from the thermostat through a copper spiral immersed in melting ice and returning it to the Dewar vessel. A temperature of 0° was achieved by continuously stirring a mixture of pure ice shavings and distilled water. The maximum variation was always within $\pm 0.01^\circ$, as measured with a mercury-in-glass thermometer calibrated at the National Physical Laboratory. The adsorbent bucket was at all times during measurements at least 12 in. below the surface of the liquid.

Procedure

After the adsorbent had been outgassed at 120° for a minimum period of 8 hours in a vacuum of $\sim 5 \times 10^{-6}$ mm. or better, the balance case was surrounded by the adsorption thermostat. After careful bulb-to-bulb distillations to remove all traces of dissolved gas from the heptane, the reservoir was immersed in its thermostat bath, the magnetic stirrer set in operation, and stopcocks E and G (Fig. 1) opened so that the bulb H became filled with heptane vapor at the pressure of the forthcoming experiment. About 30 minutes later stopcock E was closed, trap F cooled in liquid air until all the heptane in H was condensed, and stopcock G closed. The trap F, which was then allowed to warm to room temperature, thus contained enough heptane vapor to rapidly fill the volume enclosed by stopcock A, valve B, and the balance case to the pressure of the experiment. The two-phase system was, therefore, only required to replace the small amount of heptane vapor 'lost' through adsorption. After the balance case had been isolated from the pumps (stopcock A), the Hoke valve B was cautiously opened and the moment it was fully opened (taken as $t = 0$), the heptane in trap F was allowed to fill the balance case. The movement of the lower hook on the quartz spiral relative to a fixed mark on the outside of the balance case was then followed as a function of time using a cathetometer. At the end of the experiment the valve B was closed and the balance case evacuated through a series of fine capillaries (not shown in Fig. 1) before stopcock A was opened and the outgassing furnace switched on. These precautions were essential to avoid spilling the adsorbent powder by too vigorous pumping.

The Vapor Pressure of Heptane

Mündel in 1913 measured the vapor pressure of heptane between -63° and -40° C. (22). These appear to be the most recent direct pressure measurements available in this temperature range. Rossini and his co-workers have more recently reported precise measurements at temperatures from room temperature upwards (24). The extrapolated pressures from Rossini's data do not agree with Mündel's pressures. The latter used heptane which was separated from a naturally occurring turpentine. He recorded its boiling point to be 97.5° C. while the present accepted value is 98.427° C. (26).

It is possible to calculate the vapor pressure from the relative free energies of the liquid and vapor by means of the equation:

$$RT \ln P = [F^\circ(\text{sat. liq.}) - H_0^\circ] - [F^\circ(\text{gas}) - H_0^\circ] - PB,$$

where $F^\circ - H_0^\circ$ is the relative free energy and B the second virial coefficient. Accurate values of the relative free energy of the liquid from the melting point (182.562° K.) upwards have been published by Douglas *et al.* (15). The same authors have calculated

the relative free energy of the vapor from 25° C. upwards. Using their standard values of enthalpy and entropy at 298.16° K. we have calculated the relative free energy of the vapor at several temperatures below 0° C. by means of the relations:

$$-(F^\circ - E_0^\circ) = TS^\circ - (H^\circ - E_0^\circ),$$

$$H^\circ - E_0^\circ = \int C_p^\circ dT,$$

$$S^\circ = \int (C_p^\circ/T) dT,$$

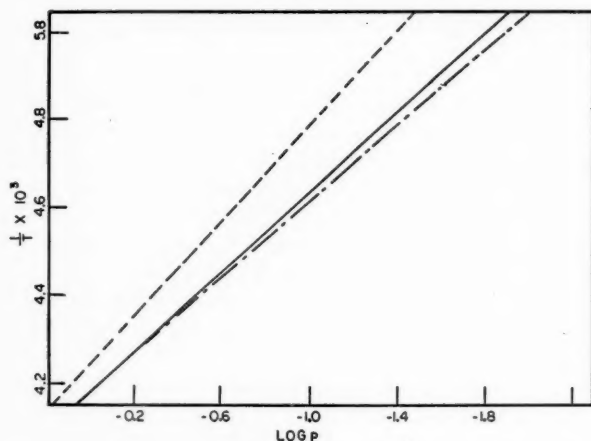


FIG. 2. The vapor pressure of heptane; $\log_{10} p$ (mm.) is plotted against $1/T$. Mündel's data, - - -; Rossini's data, - · -; calculated vapor pressure, —.

where $H^\circ - E_0^\circ$ is the relative enthalpy. To do this we have assumed that Douglas' equations for the specific heat of the vapor and for the second virial coefficient are valid below 0° C. These equations are:

$$C_p^\circ = 197.28 + 0.4498(T - 370),$$

and

$$B = -776 - 18.71e^{1.400/T}.$$

The results of these calculations are shown in Table I and appear graphically in Fig. 2 together with the vapor pressure curve from Mündel's data and the extrapolated curve from Rossini's data. It is our opinion that the vapor pressures calculated from the thermodynamic data are the most reliable values, and these are used in all the subsequent calculations.

TABLE I

T , ° K.	C_p° , joules/degree/mole	$H^\circ - E_0^\circ$, joules/mole	$S^\circ - S_0^\circ$, joules/degree/mole	$-(F^\circ - E_0^\circ)$, joules/mole	B , cm. ³ /mole	P , mm.	$\log p$
240	138.81	80389	394.54	14301	-7151	1.025	-0.0107
230	134.31	79024	388.73	10384	-9039	0.420	-0.3767
220	129.81	77704	382.87	6527	-11608	0.156	-0.8069
210	125.31	76429	376.94	2728	-17141	0.0521	-1.2832
200	120.81	75199	370.94	-1011	-21293	0.0151	-1.8211

EXPERIMENTAL RESULTS

Equilibrium Measurements

Some of the preliminary rate experiments were continued until equilibrium was established and a number of points on the adsorption isotherms gradually accumulated. However, owing to small ($\sim 1\%$) variations in the surface properties of the adsorbent, the resultant isotherms were not as smooth as was desired. More consistent results were obtained by measuring all five isotherms in a single continuous experiment, starting at 30° , proceeding up the 30° isotherm, changing to 22.5° , descending the 22.5° isotherm,

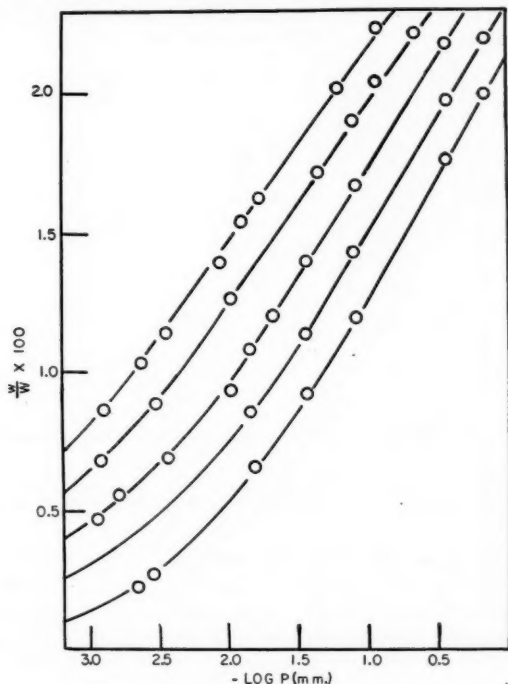


FIG. 3. Adsorption isotherms of *n*-heptane on Spheron 6.

and so on. The criterion for equilibrium was that at each point no change in the amount adsorbed should be detected over a period of 20 minutes. The results are shown in Fig. 3; the weight of heptane (w), expressed as a percentage of the weight of adsorbent (W), is plotted against the logarithm of equilibrium pressure in mm. Hg. The maximum uncertainty in the cathetometer readings was ± 0.002 cm., so the values of $100w/W$ are accurate to ± 0.004 units.

The heat of adsorption as a function of the amount adsorbed was calculated from the isotherms using the Clausius-Clapeyron equation; a similar calculation was applied to the isotherms measured under similar conditions of temperature and pressure by Smith (27) for the adsorption of heptane on graphite. The monolayer capacity of the present adsorbent ($w/W = 0.038$) was calculated from its specific surface area, taking 64 \AA^2 for the area of an adsorbed heptane molecule (20); that for Smith's graphite was

obtained by applying the 'Point B' method (16) to his four isotherms and taking the mean result. The results for the two surfaces, using these values, are compared in Fig. 4, in which the heat of adsorption is plotted against the estimated fractional surface coverage. The data for Spheron 6 have been calculated using both Mündel's vapor pressures and those derived from the thermodynamic data. The latter are in excellent agreement with Smith's data for graphite. It is interesting to note that Beebe has found for a 5% coverage on Spheron 6 a heat of adsorption of 3 kcal. per mole per $-\text{CH}_2$ group for straight-chain hydrocarbons up to pentane (4). This agrees with our value of 20.50 kcal. per mole for this surface concentration. Polley, Schaeffer, and Smith (23) have also

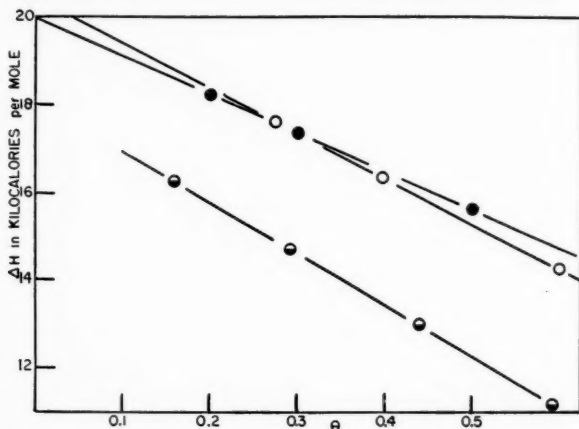


FIG. 4. The heat of adsorption as a function of surface coverage. ●, Smith's data for graphite; ○, present work using calculated vapor pressure; ◐, present work using Mündel's vapor pressure.

investigated the variation of ΔH with the number of carbon atoms in the adsorbing molecule. The interpolation of C_7 on their graph gives 20.5 kcal. per mole for heptane, in excellent agreement with our results. It is unlikely that the heat of adsorption of heptane on Spheron 6 could be 3 kcal. per mole less than its heat on graphite, which would be so if we accept Mündel's vapor pressure data.

Kinetic Measurements

The solution of the diffusion equation for the conditions prevailing in the present experiments is given by Barrer (3) as

$$[1] \quad Q = C_0 \sqrt{Dt/\pi},$$

where Q is the amount of vapor adsorbed in time t , C_0 is the concentration of adsorbed vapor on the outer layer of the powder mass, and D is the diffusion coefficient. Satisfactory and reproducible linear plots of Q versus $t^{1/2}$ were obtained between 0° and 30°C . and over a wide range of pressures; the data for various pressures at 15°C . on sample I are shown in Fig. 5. If the reasonable assumption is made that the outer layer is at all times in equilibrium with the vapor phase, then the value of C_0 may be interpolated from the appropriate adsorption isotherm and D calculated for any particular experimental condition. The equation given above was derived on the assumption that D is independent

of C , but it applies equally well when D is a function of C . In the latter case the D determined is an average value, the exact nature of the average depending on the functional relationship between D and C (9).

Two series of rate measurements were made using two different samples of Spheron 6 of approximately equal weights (0.0745 and 0.0738 g.). Twenty-four rate measurements were made with the first sample at three different temperatures, 30.2°, 15.2°, and 0.0° C., of which the six carried out at 15.2° C. are shown in Fig. 5. In the second series 18 rates

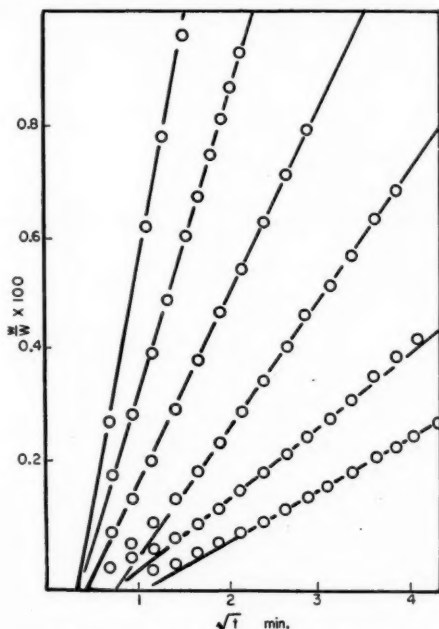


FIG. 5. The rate of adsorption of heptane on Spheron 6 at 15.2° C. and various concentrations; Fick's law is obeyed since the amount adsorbed plotted against \sqrt{t} gives a straight line. The concentrations used were: 0.0155, 0.0135, 0.0111, 0.0093, 0.0073, and 0.0059 grams of heptane per gram of charcoal.

were determined at five different temperatures, 30.0°, 22.5°, 15.0°, 7.5°, and 0.0° C. The two samples differed slightly in weight, shape, and density of packing. Because of this, the adsorption at any given temperature and pressure was slightly different for each sample. On the average, sample II adsorbed the vapor 12% more slowly than sample I.

In Fig. 6 the slopes of the Q vs. $t^{1/2}$ plots for series I are shown as a function of C_0 , the equilibrium surface concentration. If the coefficient of diffusion were independent of the concentration of adsorbed molecules on the surface over which diffusion is taking place, the data in Fig. 6 would give straight lines. The fact that the lines curve rapidly upward as C increases implies that D increases, probably exponentially, with surface coverage. During any given run D varies throughout the bed as the adsorbed concentration varies, and the value of D calculated from equation [1] is an average D which we will designate by \bar{D} . In Fig. 7 the logarithms of \bar{D} for each temperature are plotted against C_0 . The straight lines were fitted to the experimental points by the method of least squares.

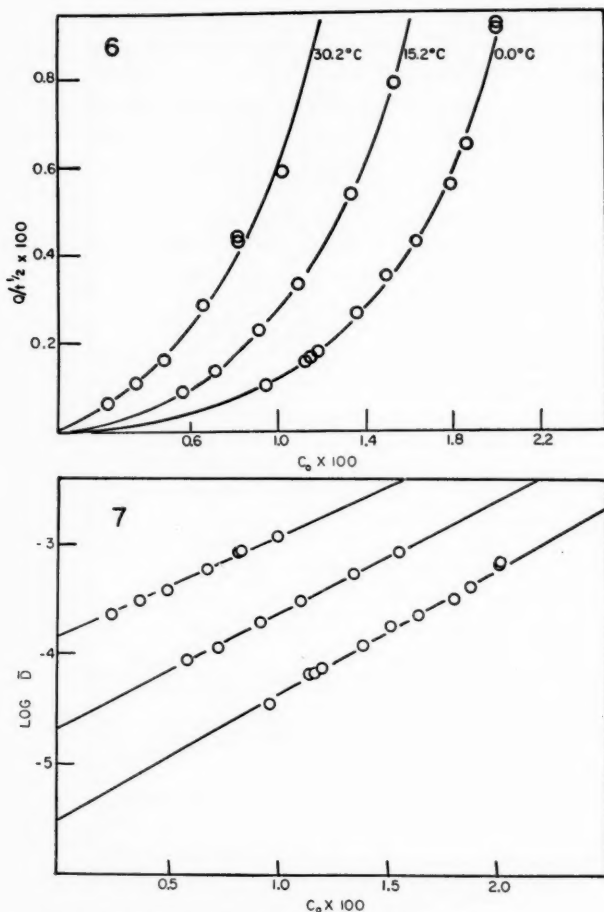


FIG. 6. The slopes of the rates of adsorption plotted against the equilibrium concentration. The data for 15.2° C. are the slopes of the lines shown in Fig. 5.

FIG. 7. The logarithm of the mean diffusion coefficient, \bar{D} , plotted against the equilibrium concentration. The extrapolation of these lines to zero concentration gives the value of \bar{D}_0 for each temperature.

The Calculation of D as a Function of C

Crank and others have developed a number of methods for calculating the concentration dependence of diffusion coefficients from data of the kind given above (9). All of these methods involve some form of approximation since the differential equation for diffusion where D depends on the concentration cannot be integrated directly (2, 8, 16).

Crank has found that the relationship

$$\bar{D} = \frac{5}{3} \frac{1}{C_0^{5/3}} \int_0^{C_0} C_0^{2/3} D dC$$

holds with an accuracy of 1% for diffusion coefficients that depend on the concentration in many different ways (10). Thus by plotting $\frac{5}{3} \bar{D} C_0^{5/3}$ against C_0 one may determine D

for any concentration by graphical differentiation. The data for series I at 15° C. treated in this way are shown in Fig. 8. The results are given in Table II. This method is known as the 'Method of Weighted Means'.

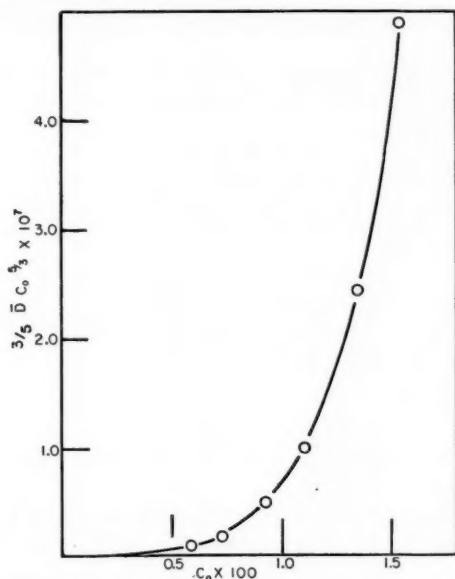


FIG. 8. The plot at 15° C. of $\frac{3}{5} D C_0^{5/3}$ vs. C_0 from which D as a function of C_0 is determined by Crank's method of "Weighted Means."

TABLE II

Data for constructing weighted curve				Conc. where tangent taken	$C^{2/3}$	Slope of tangent $\times 10^5$	$D \times 10^4$	$\log D$
Run No.	C_0	$\bar{D} \times 10^4$	$\frac{3}{5} \bar{D} C_0^{5/3} \times 10^4$					
$T = 0^\circ \text{C.}$								
8	0.00964	0.393	1.03	0.008	0.0400	2.33	0.583	-4.234
9	0.0114	0.652	2.26	0.009	0.0433	3.33	0.880	-4.055
6	0.0117	0.682	2.47	0.010	0.0464	6.00	1.29	-3.889
10	0.0120	0.749	2.83	0.011	0.0495	8.41	1.70	-3.770
28	0.0138	1.260	5.98	0.012	0.0524	12.00	2.29	-3.640
11	0.0152	1.830	10.26	0.013	0.0553	19.00	3.34	-3.463
3	0.0165	2.270	14.58					
$T = 15.2^\circ \text{C.}$								
				0.007	0.0366	1.07	1.91	-3.718
27	0.00585	0.881	0.100	0.008	0.0400	1.25	3.12	-3.506
26	0.00730	1.10	0.182	0.009	0.0433	2.10	4.85	-3.314
25	0.00930	2.03	0.500	0.010	0.0464	2.80	6.03	-3.220
24	0.0111	3.04	1.000	0.011	0.0495	3.50	7.08	-3.150
23	0.0135	5.34	2.45	0.012	0.0524	5.50	10.5	-2.979
22	0.0155	8.48	4.90	0.013	0.0553	7.50	13.6	-2.868
$T = 30.2^\circ \text{C.}$								
19	0.00235	2.50	0.063	0.005	0.0292	1.63	5.57	-3.254
18	0.00367	2.94	0.154	0.006	0.0330	3.03	9.18	-3.037
17	0.00500	3.64	0.320	0.007	0.0366	4.80	13.1	-2.882
16	0.00675	5.93	0.851	0.008	0.0400	6.60	16.5	-2.783
14	0.00835	8.83	1.82	0.009	0.0433	8.59	19.9	-2.712
13	0.00935	9.36	1.93	0.010	0.0464	11.65	25.1	-2.600
15	0.0104	10.66	3.17					

By assuming an exponential relationship between \bar{D} and C_0 one can extrapolate \bar{D} to zero concentration and obtain a value of \bar{D}_0 . This can be done from the series I data of Fig. 7. Crank has published a correction curve which gives the difference between \bar{D}/\bar{D}_0 and $(1/C_0) \int_0^{C_0} (D/D_0) dC$ for exponential dependence of D on C (10). Making use of this curve and following the procedure given by Crank we have calculated D as a function of C by this method. The data for series I appear in Table III. Values of \bar{D}

TABLE III

C_0	\bar{D}_i cm. ² /sec.	D_i cm. ² /sec.	log D
$T = 0^\circ \text{C.}$			
0.009	3.40×10^{-5}	8.33×10^{-5}	-4.079
0.008	2.62×10^{-5}	5.92×10^{-5}	-4.228
0.007	2.02×10^{-5}	4.22×10^{-5}	-4.375
0.006	1.55×10^{-5}	3.02×10^{-5}	-4.520
0.005	1.20×10^{-5}	2.06×10^{-5}	-4.686
0.000	3.24×10^{-6}	3.24×10^{-6}	-5.489
$T = 15.2^\circ \text{C.}$			
0.009	1.81×10^{-4}	4.17×10^{-4}	-3.380
0.008	1.42×10^{-4}	3.09×10^{-4}	-3.510
0.007	1.12×10^{-4}	2.30×10^{-4}	-3.638
0.006	8.80×10^{-5}	1.63×10^{-4}	-3.788
0.005	6.92×10^{-5}	1.16×10^{-4}	-3.936
0.000	2.08×10^{-5}	2.08×10^{-5}	-4.682
$T = 30.2^\circ \text{C.}$			
0.010	1.13×10^{-3}	2.40×10^{-3}	-2.620
0.009	9.22×10^{-4}	1.88×10^{-3}	-2.726
0.008	7.51×10^{-4}	1.50×10^{-3}	-2.824
0.007	6.13×10^{-4}	1.10×10^{-3}	-2.959
0.006	5.00×10^{-4}	8.05×10^{-4}	-3.094
0.000	1.46×10^{-4}	1.46×10^{-4}	-3.834

were taken from Fig. 7 in the concentration range 0.005 to 0.01. Higher values of concentration could not be used because the correction curve is only applicable below $\bar{D}/D_0 = 30$.

In Fig. 9 the results for the above methods are combined to show the exponential dependence of D on C for series I data.

The series II data (given in Table IV) were treated only by the "Correction Curve" method. The results are shown graphically in Fig. 10. In this case the measured values of \bar{D}/D_0 were generally less than 30 so that the calculated D values correspond to the experimental points.

The Calculation of Activation Energies

By use of the Arrhenius equation one may calculate, from the above data, the activation energy for diffusion as a function of surface coverage. The results of this calculation are shown graphically in Fig. 11. The equations relating activation energy and concentration for each series of data are:

$$E_I = 20,700 - 280,000C,$$

$$E_{II} = 20,800 - 294,000C.$$

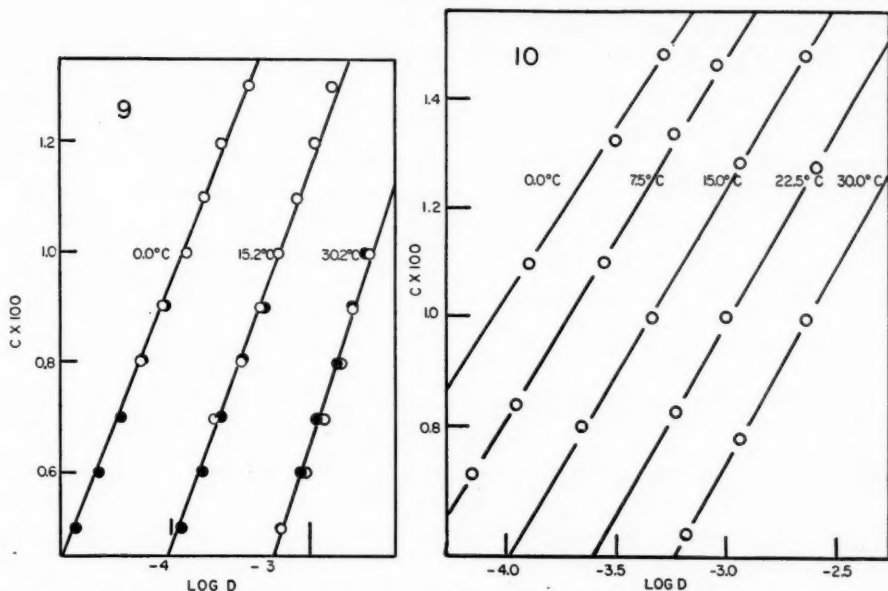


FIG. 9. The logarithm of D as a function of C for series I. ●, points calculated by weighted mean; ○, points calculated by correction curve.

FIG. 10. The logarithm of D as a function of C for series II. The correction curve method only was used.

TABLE IV

C_0	\bar{D}_1 cm. ² /sec.	D_1 cm. ² /sec.	$\log D$
$T = 0.0^\circ \text{C.}$			
0.0149	1.32×10^{-4}	4.98×10^{-4}	-3.303
0.0132	9.02×10^{-5}	3.06×10^{-4}	-3.514
0.0108	4.37×10^{-5}	1.24×10^{-4}	-3.907
0.0000	2.24×10^{-5}	2.24×10^{-5}	-5.650
$T = 7.5^\circ \text{C.}$			
0.0147	2.41×10^{-4}	8.83×10^{-4}	-3.054
0.0134	1.67×10^{-4}	5.63×10^{-4}	-3.250
0.0110	9.52×10^{-5}	2.71×10^{-4}	-3.567
0.0084	4.84×10^{-5}	1.09×10^{-4}	-3.963
0.0071	3.54×10^{-5}	6.90×10^{-5}	-4.161
0.0000	5.75×10^{-5}	5.75×10^{-5}	-5.241
$T = 15.0^\circ \text{C.}$			
0.01485	6.34×10^{-4}	2.24×10^{-3}	-2.650
0.01287	3.19×10^{-4}	1.28×10^{-3}	-2.893
0.01000	1.77×10^{-4}	4.50×10^{-4}	-3.347
0.0080	1.09×10^{-4}	2.16×10^{-4}	-3.666
0.0000	1.66×10^{-5}	1.66×10^{-5}	-4.780
$T = 22.5^\circ \text{C.}$			
0.0128	8.64×10^{-4}	2.53×10^{-3}	-2.597
0.0100	4.09×10^{-4}	9.53×10^{-4}	-3.007
0.0083	2.83×10^{-4}	5.80×10^{-4}	-3.237
0.0000	4.17×10^{-5}	4.17×10^{-5}	-4.380
$T = 30.0^\circ \text{C.}$			
0.0100	9.94×10^{-4}	2.28×10^{-3}	-2.642
0.0079	5.51×10^{-4}	1.32×10^{-3}	-2.879
0.0060	3.92×10^{-4}	4.46×10^{-4}	-3.351
0.0000	1.00×10^{-4}	1.00×10^{-4}	-4.000

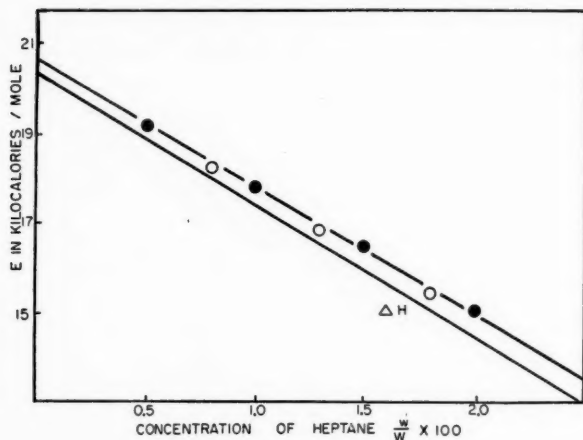


FIG. 11.⁴ The activation energy for diffusion plotted as a function of concentration. The heat of adsorption calculated from the isotherms is included for comparison. ●, series I data; ○, series II data.

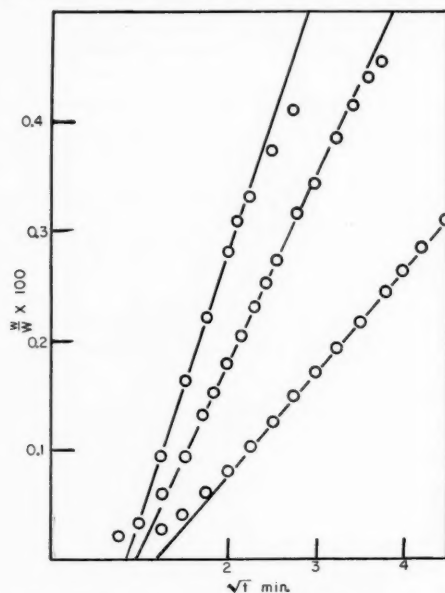


FIG. 12. The rate of adsorption of heptane on Spheron 6 which had already been equilibrated to various heptane concentrations. Curves I, II, and III were equilibrated to 0.0088, 0.0070, and 0 grams of heptane per gram of charcoal respectively.

Further Rate Measurements

A number of rate measurements were made where the heptane was allowed to adsorb on a surface which had been previously equilibrated to some predetermined value of C_0 . As would be expected the rates of adsorption for equal concentration gradients were very much higher than when adsorption occurred on a completely bare surface. The data

for several conditions of temperature and concentration appear in Table V while Fig. 12 shows the rates for a constant concentration gradient of 0.060 adsorbed on initial concentrations of 0.088, 0.070, and 0.

TABLE V

Run No.	$T, ^\circ\text{C.}$	C_0	C_1	$D, \text{cm.}^2/\text{sec.}$
27B	7.5	0.0070	0.0130	1.55×10^{-4}
26B	15.0	0.0070	0.0130	2.89×10^{-4}
25B	22.5	0.0070	0.0130	6.17×10^{-4}
21B	0.0	0.0088	0.0150	1.31×10^{-4}
22B	7.5	0.0088	0.0150	3.01×10^{-4}
23B	15.0	0.0088	0.0150	5.83×10^{-4}

DISCUSSION

The methods of calculating D as a function of concentration involving the fitting of data to generalized curves, the use of correction curves, and the determination of slopes and intercepts of lines which are not entirely free from ambiguity cause some uncertainty in the final results. However, despite this, the over-all picture is clear, that is, that the activation energy for the movement of the heptane into the bed of Spheron 6 is not significantly different from the heat of adsorption. From this we conclude that the rate-determining step in the adsorption of heptane on Spheron 6 is one which involves desorption of the heptane molecule from the surface.

The particles of Spheron 6 are known to be approximately spherical, each sphere being composed of a number of similar graphite crystallites (6, 17). From the particle size distribution a value of approximately 250 Å is obtained for the arithmetic mean particle diameter (25). If the density of a spheron particle is 2.2 g. per cc., then the average width of the spaces between the particles must be 500 Å to satisfy the density of packing used in these experiments, i.e. 0.075 g. occupying a volume of 0.25 cc. There is, therefore, ample room for the passage of a heptane molecule, the Sutherland collision area of which is given by Melaven and Mack (21) as 26.7 Å (2). The mean free path of *n*-heptane vapor at 15°C. and 0.05 mm. pressure (the average value in the present work) is approximately 0.2 mm., which is 4×10^3 times the average distance between the spheron particles. It is, therefore, concluded that the vapor cannot enter the spheron bed by Poiseuille flow but must move by Knudsen flow.

When the vapor is first admitted to the adsorbent there is nothing to prevent the rapid establishment of adsorption equilibrium on the uppermost particles of the powder mass. However, a heptane molecule is able to penetrate only by pursuing a zig-zag path brought about by collisions with adsorbent particles. Since heptane is quite strongly adsorbed under the present experimental conditions, a heptane molecule striking a vacant adsorbent site will become adsorbed and remain so until it can acquire sufficient energy to re-evaporate. The energy necessary for evaporation is equal to the differential heat of adsorption, the value of which depends on the fractional surface coverage of the particular element of surface from which the molecule evaporates.

When a molecule evaporates it may leave the surface in any direction, the probability of it taking a given direction being given by the Knudsen cosine law. As long as a concentration gradient exists, however, more molecules will move with a forward component than with a backward one, so that a net forward flow results. The rate of attaining equilibrium will depend not only on the concentration gradient but also on the time

the molecules moving into the bed spend 'resting' in the adsorbed state. This latter factor is temperature dependent so that for the same concentration gradient, adsorption takes place quicker at higher temperatures. Since the activation energy necessary to desorb is the greater the more sparsely the surface is covered, the more advanced a molecule is the more slowly it will move into the carbon bed. This will cause a steeper concentration gradient towards the front of the advancing heptane than if D were independent of surface coverage. From the dependence of D on C one can calculate the distribution of heptane in the charcoal bed at any time after exposure to the vapor. This has been done, by the method of Crank and Henry (11), for a heptane pressure of 0.002 mm. and a temperature of 0° C. The results are shown graphically in Fig. 13.

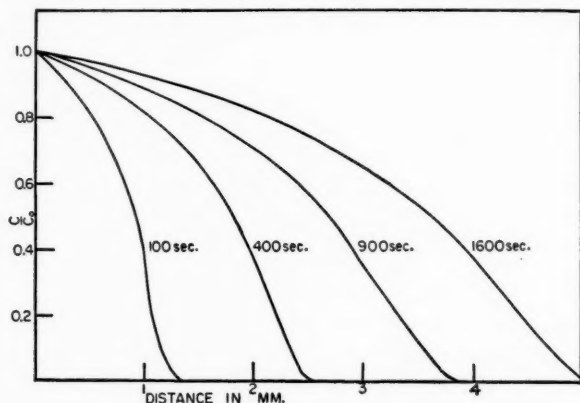


FIG. 13. The concentration distribution of *n*-heptane in a 5 mm. bed of Spheron 6 at various times after exposure to heptane vapor at a pressure of 0.002 mm. at 0° C.

Confirmation of the proposed mechanism comes from the few data obtained when heptane was allowed to move into a bed already partly but uniformly covered with adsorbed vapor. At 15° C. for instance, and a concentration gradient of 0.006, \bar{D} increased from 7.08×10^{-5} for a bare surface to 31.0×10^{-5} for a coverage of 0.007 and 58.3×10^{-5} for a coverage of 0.0088 g./g. From the linear variation of $\log \bar{D}$ with C one can predict that these values should be 35.5×10^{-5} and 59.7×10^{-5} .

It is not difficult to reconcile the model with the theoretical results of Crowell and Young (12, 13), who have shown that there is virtually no barrier to the translation of an argon atom on a uniform basal plane of graphite. It is likely that a considerable potential energy barrier exists across the points of contact of cotangent Spheron 6 particles where, to cross from one particle to its neighbor, a molecule must pass along a narrow crevasse within the potential fields of both surfaces (that of the particle which it is leaving and that of the particle to which it is destined). Thus, even if an appreciable number of adsorbed molecules are able to surmount the potential barrier, which is of the same order of magnitude as the heat of adsorption, the points of contact are so small in area and few in number that a negligible proportion of adsorbed molecules are able to make use of this mode of transport.

These considerations do not, of course, apply to migration across the boundaries separating the graphitic crystallites which compose each Spheron 6 particle, a process which probably requires a somewhat lower activation energy. Thus, while migration

over the surfaces of the individual particles may play an important role in the establishment of adsorption equilibrium, it is not rate-determining.

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A STUDY OF SULPHATE IN NITROCELLULOSE USING S³⁵O₄⁻ AS TRACER¹

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ABSTRACT

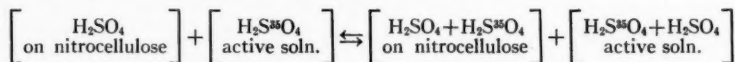
S³⁵O₄⁻ has been used to show that the residual sulphur in nitrocellulose is not held by adsorption on the surface, as sulphate. Evidence has been obtained to support the view that the sulphur which is not removed by washing after nitration and subsequent stabilization is present within the fibrous structure.

INTRODUCTION

It is well known that commercial nitrocellulose contains a small amount of residual sulphur, representing about 0.05–0.10% of the product, expressed as sulphuric acid, which resists removal by the usual stabilizing procedures and to which the tendency of nitrocellulose to instability in storage may be attributed. Many authorities suggest that the sulphur is chemically bound (7, 10, 11) through an ester linkage, but the alternative suggestion that this residue is adsorbed has also been made (19). More recently Smith (13) has suggested that the residue is not adsorbed in the usual sense, but that there is an inclusion of free sulphuric acid within the fiber. This could result from swelling during the initial stages of nitration, which would permit entry of the acid, and subsequent shrinking during drowning, washing, and stabilization. Reeve and Giddens (16) have also suggested that free sulphuric acid might be held within the fibrous structure and that its retention would not make the assumption of chemical bonding essential but that it might be explained on a basis of selective permeability of the membrane.

Relatively little work has been done to determine whether the adsorption mechanism is the correct one. The object of this investigation was to apply radioactive tracer techniques to the problem.

If the residual sulphuric acid were merely adsorbed, it would be expected that if the material were brought into contact with a further supply of sulphuric acid in which the sulphate ion was tagged with radioactive sulphur, S³⁵, exchange would take place and as a result the nitrocellulose sample would acquire activity while the original active preparation of sulphuric acid would decline in activity.



Since the molecular species involved are identical, there seems no reason to suppose that exchange would not be complete in the case of adsorption of sulphuric acid on the nitrocellulose. If the acid were held by inclusion within the fibers, exchange might be expected to depend on the possibility of swelling of the fibers. The ultimate equilibrium achieved would depend upon the diffusion rate and thus upon the elapsed time, the concentration, and the temperature at which the experiment was performed.

The first and principal portion of the work to be described consisted in the placing of samples of nitrocellulose of known weight and sulphur content into carrier-free solutions of active sulphuric acid of known activity. The system was shaken, continuously at room temperature and at frequent intervals at higher temperatures, and at definite time inter-

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vals aliquots of the active solution were withdrawn and their activity determined. The nitrocellulose samples used were both stabilized and unstabilized, damp and dry. The detail of this work will be found in the experimental section of this account.

A second and briefer experimental series was conducted on samples of nitrocellulose recovered after the exchange experiments had been completed, to determine the magnitude of any acquired activity and any variations it might exhibit with varying treatment of the nitrocellulose.

EXPERIMENTAL

Materials

Sulphur-35.—This was obtained as carrier-free $\text{H}_2\text{S}^{35}\text{O}_4$ in dilute hydrochloric acid from Atomic Energy of Canada Limited. The activity was 1 mc. per ml. The acid contained no detectable inactive sulphate or sulphur, and half-life and absorption half-thickness agreed with values given in the literature (1).

Nitrocellulose.—This took the form of nitrated cotton linters. Four samples were employed:

Sample A. Unstabilized—654 mg. H_2SO_4 per 100 g.

Sample B. Stabilized—60 mg. H_2SO_4 per 100 g.

Sample C. Unstabilized—412 mg. H_2SO_4 per 100 g.

Sample D. Stabilized—125 mg. H_2SO_4 per 100 g.

Samples A and B were of the same batch, manufactured February 4, 1954. Sample B was stabilized by refluxing for 30 hours with water. Both sulphate analyses were by Canadian Armament Research and Development Establishment. Samples C and D were not of the same batch. Sample C was manufactured March 28, 1955, and Sample D on April 1, 1955. Sample D was stabilized by boiling with distilled water for 9 hours, the water being changed every 3 hours. Samples C and D were shipped in 2.0 *N* NaCl solution. The above material was supplied by Canadian Armament Research and Development Establishment, Valcartier, Quebec.

Barium chloride.—This material was crystalline $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ of A.C.S. Reagent Grade. It was used as supplied by Anachemia Chemicals Limited, Montreal.

Counting equipment.—A thin window Geiger tube, with window thickness 1.4 mg. per cm^2 , was employed in conjunction with a Nuclear Instrument and Chemical Corporation scaler.

Storage and Washing of Nitrocellulose

The samples as received were well agitated with distilled water in a 4-liter beaker, using 3 liters of water for each of four to five washings. The material was stored in distilled water and the unstabilized samples were washed every 2 or 3 days. Stabilized samples of nitrocellulose were usually washed at the same time, though frequent washing is not so important in this case.

The samples that were forwarded packed in 2.0 *N* sodium chloride solution gave great difficulty. Continuous washing in distilled water for 48 hours was recommended but could not reasonably be arranged for. These samples were washed four to five times daily, with vigorous stirring, in 3-liter quantities of distilled water, the samples being left in the water to equilibrate between changes. It was found that 30 such washings were required before the wash water, on being tested with silver nitrate, showed no more than a faint opalescence.

When samples were required for experimental purposes the whole supply of a given nitrocellulose was transferred to a large beaker and washed three times with 2 liters of distilled water, vigorous stirring being given. After each wash, the material was poured onto an 8-inch Büchner funnel and pressed well down. After the third washing and pressing, the required sample was taken.

Sampling of Nitrocellulose

When moist samples were required, a bulk of nitrocellulose was squeezed as dry as possible, a moist sample taken from the center of the mass and placed in a weighing bottle, and after weighing a suitable portion removed for the experimental work. The balance of the material was dried to constant weight, either for 10 hours in a vacuum oven at 42° C. or for 14 hours over phosphorus pentoxide in a vacuum desiccator at room temperature (8, 9), and the moisture content calculated. Each of these drying methods had been shown to give reproducible results. Dried nitrocellulose, obtained as described, was employed as dry samples and also in determinations of sulphur content.

Determination of Sulphate in Samples

The modification of Dunnicliff's method, as described by Kierstead and Myers, was used (9).

"Infinite Thickness" for Labelled Barium Sulphate Precipitate

"Infinite thickness" was determined to be 30–35 mg. of barium sulphate per sq. cm. The value is in good agreement with the suggestions of Libby (12) and current estimates of the range of S^{35} radiation (20). Weights of precipitate used for counting were made just sufficient to exceed this value (1).

Method

Samples of nitrocellulose were shaken with dilute solutions of $H_2S^{35}O_4$ for successive known periods, and aliquots of the active acid were removed at the end of each period. The aliquots were added to fixed quantities of carrier sulphuric acid and the whole precipitated as barium sulphate, which was filtered in such a way as to give a disk of reproducible dimensions. The activity of each disk was then determined.

Having comparison disks prepared from the active acid prior to addition of nitrocellulose, it was felt that any significant change in activity due to exchange of active sulphate with inactive sulphate residing upon the nitrocellulose could easily be followed. In order to make the method sensitive the active acid was used carrier-free, and the total number of active atoms present in the acid was made about 10^6 times as small as the number of inactive sulphur atoms present in a suitable sample of the most highly stabilized nitrocellulose. At the same time, it was necessary to ensure that sufficient activity was present so that removal of a very small aliquot, insufficient to affect the total concentration of activity too greatly, would still give an adequate count when precipitated as barium sulphate.

Trial experiments showed that a sample of nitrocellulose of convenient size to shake in a stoppered tube of 30 ml. capacity had a dry weight of about 0.15 g., while it required a volume of 10 ml. of liquid to give adequate free liquid for removal of aliquots.

The tubes employed were made from 24/40 standard taper outer joints, suitably sealed off and provided with ground glass stoppers.

Prior to use, the glass tubes were cleaned with acid and alkali, followed by five scrub-

In order to ensure that any change in activity noted during an experiment was due to exchange with inactive sulphate and not to adsorption upon the glass surface, when the active acid had been placed in the tubes they were stoppered and shaken under the conditions of the particular experiment for $\frac{1}{2}$ hour before the initial reference aliquot was removed.

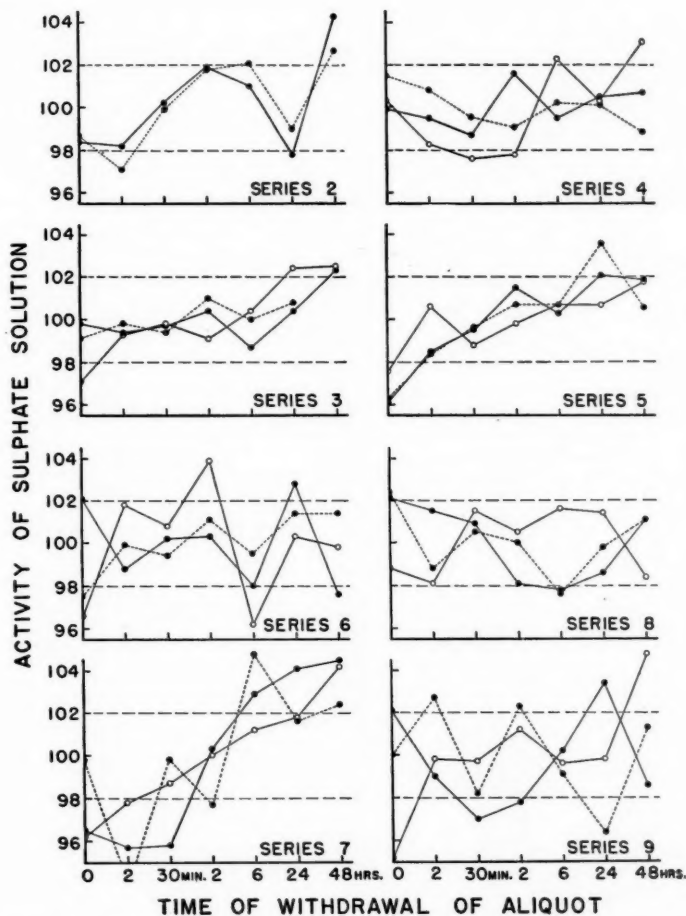


FIG. 1. Variation with time of activities of solutions in contact with nitrocellulose. Series 2-9 as in Table I. The activity of each aliquot is expressed as a percentage of the mean activity of all aliquots taken from a particular sulphate solution (see Table II). Key: unstabilized nitrocellulose —●—●—●—●—●—; stabilized nitrocellulose —●—●—●—●—●—; blank —○—○—○—○—○—.

The nitrocellulose sample was then added, and the tube stoppered and shaken. Since ovens were used for the runs carried out at 42° and 80° C., the temperature was not well controlled during the 2-minute period prior to the removal of the first aliquot. For all other periods of time the ovens were observed to vary only by $\pm 1.0^\circ$ C.

For experiments made at room temperature shaking was continuous, a Burrell wrist-action machine being used. Those experiments carried out at higher temperatures did not permit use of this method, but the tubes were hand shaken at frequent intervals.

In general, aliquots were removed from the active solution after 2 and 30 minutes, and 2, 6, 24, and 48 hours. As previously mentioned, the initial volume of active acid decided upon was 10 ml., and the aliquots were withdrawn with a 100 λ micropipette. In all experimental series other than the first two a blank was run and aliquots withdrawn from it at the same intervals as with the samples being investigated.

The radioactive sulphate was precipitated using 4.0 ml. 0.202 *N* sulphuric acid as carrier and 7.0 ml. 0.2 *N* barium chloride solution plus hydrochloric acid. Precipitates were digested on the steam bath for $\frac{1}{2}$ hour and allowed to stand overnight prior to filtering. The apparatus used for filtering had a filter disk of porous stainless steel (15) and Whatman filter paper No. 40 was used. The surface area of the disk was 2.69 sq. cm. By strict adherence to a standardized procedure, counts on various samples agreed to within the limits to be expected for radioactive samples. Ten thousand counts were usually measured.

The results of the experiments are summarized graphically in Fig. 1, in which the activity relative to the mean is shown against an arbitrary time scale. These diagrams are intended merely to illustrate that the results obtained were random in distribution.

TABLE I
EXCHANGE EXPERIMENTS PERFORMED WITH NITROCELLULOSE AND $\text{S}^{35}\text{O}_4^{=}$

Series	Sample	Conditions	Temp., ° C.	Elapsed times	% Standard deviation
1 (i)	A	Oven-dried	24	0, 1, 2, 4, 8, 16, 32 min.	2.08
(ii)	B	"	24	"	1.30
2 (i)	A	"	42	0, 2, 30 min.; 2, 6, 24, 48 hr.	2.04
(ii)	B	"	42	"	2.34
3 (i)	A	"	80	"	0.70
(ii)	B	"	80	"	1.12
(iii)	Blank	—	80	"	1.83
4 (i)	C	Oven-dried	24	"	0.94
(ii)	D	"	24	"	0.96
(iii)	Blank	—	24	"	2.24
5 (i)	C	Oven-dried	80	"	2.29
(ii)	D	"	80	"	2.21
(iii)	Blank	—	80	"	1.42
6 (i)	C	Vacuum dried	28	"	1.41
(ii)	D	"	28	"	2.01
(iii)	Blank	—	28	"	2.74
7 (i)	C	Vacuum dried	42	"	3.51
(ii)	D	"	42	"	3.95
(iii)	Blank	—	42	"	2.76
8 (i)	C	Moist	26	"	1.63
(ii)	D	"	26	"	1.83
(iii)	Blank	—	26	"	1.62
9 (i)	C	Moist	42	"	2.32
(ii)	D	"	42	"	2.36
(iii)	Blank	—	42	"	2.82
Mean					2.02

The points are joined solely to facilitate following the readings obtained for a given sample. The standard deviations of the activities with respect to the mean are recorded as a percentage in the last column in Table I. It will be noted that the mean of the standard deviations is 2.02%. Also, that the deviations for the blank experiments vary as widely as do those for the experiments involving nitrocellulose, and that we might expect a deviation of 1% on the basis of counting statistics alone. Consequently, we feel that we can say that there was no appreciable exchange under the conditions of the experiments, i.e., using tracer quantities of $S^{35}O_4^{=}$, times up to 48 hours, and temperatures from 24° to 80° C.

The reversibility of adsorption has been experimentally established in numerous cases, and there would seem to be no reason to expect that sulphate adsorption on nitrocellulose would form an exception (3, 4, 5, 6, 18). It thus seems highly probable that had the sulphate of the nitrocellulose merely been adsorbed in the physical sense, it would have undergone a considerable and easily measurable exchange under these conditions. The fact that it did not seems to indicate quite definitely that the residual sulphur is not held by adsorption as sulphate. This does not, of course, rule out the possibility that the sulphuric acid may be held by occlusion, as suggested by Smith.

TABLE II
TYPICAL EXCHANGE EXPERIMENT USING NITROCELLULOSE AND $S^{35}O_4^{=}$
Series 4 (i), (ii), (iii)—Temp., 24° C. Samples C and D, oven-dried
Weights: Sample C, 0.1543 g.; Sample D, 0.1544 g.

Sample	Elapsed time	Wt. of $BaSO_4$, mg.	Net count Δ , reg./45 min.	Activity relative to mean = 100
C	0 min.	94.7	150.75	101.5
	2 min.	95.5	149.69	100.8
	30 min.	95.0	147.72	99.5
	2 hours	96.4	147.09	99.1
	6 hours	96.7	148.75	100.2
	24 hours	96.8	148.61	100.1
	48 hours	97.6	146.84	98.9
	Mean value of net count 148.49			S.D. = ± 1.4 (0.94%)
D	0 min.	96.6	147.99	99.9
	2 min.	95.2	147.44	99.5
	30 min.	97.0	146.19	98.7
	2 hours	96.8	150.55	101.6
	6 hours	95.7	147.53	99.5
	24 hours	95.9	149.00	100.5
	48 hours	97.1	149.19	100.7
	Mean value of net count 148.27			S.D. = ± 1.45 (0.96%)
Blank	0 min.	96.2	147.45	100.3
	2 min.	95.0	144.31	98.3
	30 min.	96.6	143.38	97.6
	2 hours	94.1	143.91	97.8
	6 hours	95.6	150.39	102.3
	24 hours	96.0	147.48	100.3
	48 hours	97.3	151.80	103.1
	Mean value of net count 146.97			S.D. = ± 3.28 (2.24%)

Δ , 1 register = 64 counts.

The diagrams relating activity and time, though indicating that the number of points lying within the statistical limits is appropriate for a series of values which should all be of the same magnitude, do occasionally tend to suggest a slight increase in activity

with time. Since the trend is followed by the blank determinations in these cases, it would, at first sight, seem reasonable to attribute the effect to evaporation losses.

All activity values appropriate to a given time interval were next averaged, and while these average values still lay between the standard deviation limits they showed a definite increase in activity with time.

The capacity of nitrocellulose to hold water is extreme, and a sample squeezed "dry" may still retain as much as 25% of water by weight. Thus, since the majority of determinations made in this work involved dry samples, water absorption may well account for the tendency to increasing activity, particularly since plotting the mean values of activity against time indicated that the rate of increase was greatest during the early stages of a run. The much reduced rate later observed might be the result of evaporation losses. It would seem that the apparent steady increase in activity shown by the blank in Series 7 was the result of some individual circumstance obtaining in this case, since the experimental temperature was 42° C. and neither of Series 3 or 5, both carried out at 80° C., shows such a definite gain on the part of the blank.

One would expect such an effect due to water absorption to be much less marked when moist samples were examined, and this is indeed the case in Series 8 and 9.

These results are also confirmatory of suggestions which have been made that sulphuric acid is not adsorbed physically by nitrocellulose (14), since, if it were, a fall in activity would have been expected in these experiments, even though no exchange might be taking place.

Extended Hydrolysis of Stabilized Nitrocellulose

Robertson, in reporting his early work on the stabilizing of nitrocellulose (17), pointed out that a satisfactory method must be rapid and produce minimum degradation of the material and fall in nitrogen content. It, therefore, appeared of interest to determine how a stabilized sample behaved on further boiling treatment.

To this end, a fairly large portion of Sample B, containing 60 mg. H_2SO_4 per 100 g., was placed in a 2-liter flask fitted with thermometer, stirrer, and reflux condenser. One liter of distilled water, which had been tested for sulphate, was added and the material digested with continuous stirring for 24 hours. It was not found possible to reproduce the beating action of a commercial stabilizer, but the contents of the flask were stirred in the top by a rotating stirrer and in the bottom by a magnetic stirrer, the two producing considerable turbulence. The temperature was maintained at 90° C. to 95° C.

After 24 hours the water was poured off and retained, and a further liter of distilled water was added to the flask. The operation was continued for a further 24 hours and then the second batch of extract was added to the first, the residual nitrocellulose being well washed and the washings added to the combined extracts. The extract was carefully evaporated down to small volume, treated with concentrated nitric acid and potassium chlorate, and evaporated to dryness to oxidize any organic matter in suspension or solution. Concentrated hydrochloric acid was then added and evaporation to dryness repeated. After the residue was dissolved in distilled water, sulphate was determined (1).

Sample B was employed as being the most highly stabilized available, and though it was old, it had been regularly washed and showed no visible signs of decomposition.

After 24 hours' refluxing, decomposition was pronounced, the material being quite yellow and showing some degradation. After the second period of reflux, the color was

brown-yellow, and degradation was such that the fibrous network of the sample had completely disappeared. The residue was finely divided and soft to the touch.

The barium sulphate recovered corresponded to a sulphuric acid content of 52 mg. per 100 g. of sample, or 87% of the residual H_2SO_4 originally present.

Therefore the residual sulphate can be removed by extending the stabilizing treatment only at the expense of degradation and decomposition of the nitrocellulose. The results are similar to those reported by Chédin and Tribot, who found that when nitrocellulose was boiled with water for an extended period of time, most of the residual sulphuric acid came off in the first 90 hours (2). An approximate value for the removal after 48 hours, taken from their figures, is 85%, which is in good agreement with the figure found above.

Examination of Recovered Samples of Nitrocellulose

Since the work done by measuring activity of the $\text{H}_2\text{S}^{35}\text{O}_4$ solution had indicated no significant exchange with the sulphate present in the nitrocellulose, the samples employed in exchange series 7 and 9, together with a pair of oven-dried samples, were recovered, washed, dried, and counted with the object of determining whether any activity was resident upon them.

The washing method adopted was shaking for 4-5 minutes with 25 ml. of distilled water in a stoppered tube, five such washings being given. The samples were then filtered on a small Hirsch funnel, well pressed, and dried over phosphorus pentoxide in a vacuum desiccator. They were then worked by hand into circular pads, as nearly as possible of the same diameter as the barium sulphate disks previously counted.

It has been suggested that residual sulphate present in cellulose acetate is entirely in the form $\text{R.SO}_4\text{H}$, and that complete drying of cellulose acetate causes splitting off of the sulphate-containing groups (9). For comparison purposes, therefore, some recovered cellulose acetate samples were also examined. These samples, having been counted after recovery as described above, were in each case soaked again in distilled water, washed, collected, and dried, the object of this operation being to determine whether the original drying had freed any of the sulphate groups which should then be washed off by this second process. The results are shown in Table III.

TABLE III
SAMPLES RECOVERED OR SEPARATELY TREATED AT 42° C.

Series No.	Sample	Condition	Wt. recovered (mg.)	Net count (reg./40 min.)	Appt. sp. act. (c.p.m./mg.)	Ovendry wt. after soaking (mg.)	Net count (reg./40 min.)	Appt. sp. act. (c.p.m./mg.)
7	C	Vacuum dried	134.9	8.59	0.102	123.4	5.80	0.075
	D	Vacuum dried	135.9	7.50	0.088	125.3	5.25	0.067
9	C	Moist	134.9	12.13	0.144	125.0	9.93	0.127
	D	Moist	135.1	10.67	0.127	127.0	8.66	0.109
Additional A	C	Oven-dried	143.0	0.54	Neg.	—	—	—
	D	Oven-dried	146.8	1.17	Neg.	—	—	—
B	Cell. acetate	Moist	24.0	41.64	2.78	16.3	4.14	0.41
	Cell. acetate	Dry	56.9	3.29	0.092	—	—	—

When it was found that slight activity did reside upon these recovered samples, a further series of similar experiments was conducted under different conditions of temperature. The results obtained (Table IV) showed significantly higher activities than

TABLE IV

Ref. No.	Sample	Condition	Temp., °C.	Wt. recovered (mg.)	Net count (reg./40 min.)	Appt. sp. act. (c.p.m./mg.)	Vac. dried wt. after soaking (mg.)	Net count (reg./40 min.)	Appt. sp. act. (c.p.m./mg.)
1	C	V.d.*	28-32	125.0	16.95	0.217	122.0	16.00	0.210
2	D	"	28-32	124.4	20.10	0.259	120.3	17.90	0.238
3	C	"	80	127.0	20.71	0.261	124.1	20.41	0.263
4	D	"	80	123.8	23.08	0.298	120.1	24.16	0.321
5	C	Moist	28-32	110.4	26.78	0.388	99.6	24.37	0.392
6	D	"	28-32	89.6	26.96	0.481	86.2	26.37	0.489
7	C	"	80	117.1	33.93	0.463	96.7	28.73	0.475
8	D	"	80	86.5	22.32	0.432	77.9	21.46	0.442

*V.d.—vacuum dried.

had earlier been obtained, but the recovered samples also showed considerable evidence of decomposition, having been stored for some time under rather unfavorable conditions.

It was felt that the change in behavior accompanying decomposition suggested that the activity might be within the cells of the fibers and that therefore cell rupture and subsequent washing might cause a decline in activity.

Some samples were therefore torn apart extensively under 5 ml. of cold water, using steel tweezers. The tearing was carried out for at least 2 hours until each sample had completely lost its reticulate structure and only very finely divided material remained. This treatment must have caused the fracture of a moderate proportion of the cells. These teased samples were washed, separated by centrifuging, dried, worked into pads as before, and counted. The results obtained are shown in Table V.

TABLE V

Ref. No.	Initial appt. sp. act. (c.p.m./mg.)	Wt. recovered after tearing (mg.)	Net count (reg./40 min.)	Appt. sp. act. (c.p.m./mg.)
1	0.210	109.1	10.41	0.153
7	0.475	94.0	22.47	0.383
8 (a)	0.442	74.8	18.33	0.392
(b)	0.392	70.2	14.09	0.321

At all stages the recovered dried material was weighed so that the apparent specific activity could be determined. These activities could then be compared satisfactorily with one another since changes were not simply the result of loss of material during manipulation. Correction for decay was also made. Nevertheless, the results are not considered to be more than indicative, as the likelihood of working the different samples into exactly similar pads was small.

First, it will be noticed that moist cellulose acetate showed a specific activity about 30 times greater than the dried material, and further, that after soaking, drying, and again recovering, the specific activity fell to about one-seventh of the original value. These results are in agreement with the view that the sulphate groups are split out on complete drying.

The first results using nitrocellulose, shown in Table III, indicated much lower specific activities, which were of the same order for both the stabilized and unstabilized samples, though the sulphate content in the latter case was four times that in the former. Soaking and drying also caused a decline in the specific activities, though not so extensive as in the case of cellulose acetate. Further, the ratio of the specific activities of moist cellulose acetate and moist stabilized nitrocellulose was 22:1, while that of the respective sulphur contents was 17:1. Since the cellulose acetate was much more finely divided than the nitrocellulose and its sulphate content therefore more accessible to the active acid, these similarities in behavior are suggestive that the sulphate might be in the same condition in both cases. Even though the sulphuric acid might have penetrated the cellular structure as the result of swelling during immersion in the strong nitrating acid there seems to be no greater likelihood of its remaining uncombined than its reacting with hydroxyl groups directed within the cell. The fact that the activities of stabilized and unstabilized samples were of the same order also suggests that a particular fraction of the residual sulphur was concerned with the activity. Removal of the sulphate present in stabilized nitrocellulose can also be effected only at the expense of degradation.

The figures given in Tables IV and V support these suggestions. The higher specific activities noted in Table IV would be expected if partial decomposition had resulted in some degradation and therefore greater accessibility of sulphate groups. Also it will be observed that the moist samples showed notably higher activities than the dried, in agreement with the suggestion that drying causes splitting off of sulphate groups, and any activity associated with such groups would be washed away during the preparation of the samples for counting.

After tearing, a decline in activity of about 25% was observed in each case, and in the case of a sample torn in two stages, a decline was observed at each stage.

CONCLUSION

From the foregoing, it seems to be definitely established that the residual sulphur in the nitrocellulose is not held, as sulphate, by adsorption. The residual sulphate can be removed by extending the stabilizing treatment but only at the expense of degradation and the decomposition of the nitrocellulose. This fact, supported by the results obtained from investigation of the activity of nitrocellulose which has been in contact with active sulphuric acid, suggests that the residual sulphate is present within the fibrous structure.

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A SYNTHESIS OF PORPHOBILINOGEN¹

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ABSTRACT

The pyrrole *Ib* has been converted by several routes into 5-carboxy-porphobilinogen (*IIe*), the lactam of which is easily decarboxylated to porphobilinogen lactam (*IVc*). Hydrolysis of the latter gives porphobilinogen (*V*).

Porphobilinogen (*V*) (1) is an intermediate in the biosynthesis of heme and occurs in the urine of patients with acute porphyria. Its Knorr synthesis from δ -amino-levulinic acid has been carried out both enzymically (7) and by a purely chemical method (16). Also, although porphobilinogen was not isolated, paper chromatography indicated that it was formed by the decarboxylation of 5-carboxy-porphobilinogen (*IIe*) (15). The latter was synthesized by Prasad and Raper (14) from *Ia* (11) over $I(X = CH_2.OH)$, *Ib*, *Ic*, and the free base *Ie*.

We have reported the conversion of *Ia* through *Ib* and *IIb* into *IIc*, which took up 2 moles of hydrogen in dilute ammonia over palladium black (9). The reduction product formed stable colorless needles and was presumed to be 5-carboxy-porphobilinogen (*IIe*). It was not reported because the analyses were low and variable and because it could not at the time be satisfactorily characterized.

The same product (*IIe*) has now been obtained from *Ib* (9) using the same reactions in different orders and first converting it into the oxime *Ic*. This was hydrolyzed to the known *IIc* (9), which was reduced as above to *IIe*. Alternatively, either *Ic* or the nitrile *Id* obtained from it were reduced in ethanolic hydrochloric acid over palladium to the hydrochloride of *Ie*. When *Ic* was reduced in alcoholic ammonia the product was the lactam *III*, also obtained from the hydrochloride of *Ie* with alkali. Both the hydrochloride and the lactam also gave *IIe* on alkaline hydrolysis. The over-all yields of *IIe* from *Ia* by these different routes are similar, but *Ic* and the hydrochloride of *Ie* are the optional intermediates most readily isolated.

However synthesized, the infrared spectra of the 5-carboxy-porphobilinogen (*IIe*) in Nujol mull showed inconsistent differences and the carbon analyses remained low and variable. This could not be due to incomplete reduction of the oximino group because the reduced intermediates were well characterized and analyzed well. The nature and purity of the 5-carboxy-porphobilinogen is no longer doubted because all samples give identical X-ray powder photographs if not allowed to dry, behave identically on paper chromatography, and give the same well-characterized lactam (*IVb*). We assume that unstable hydrates or polymorphic forms were responsible for the difficulties.

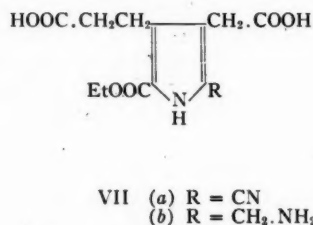
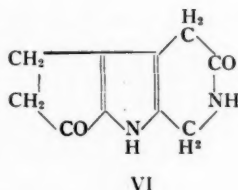
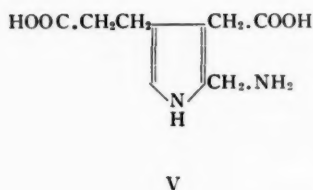
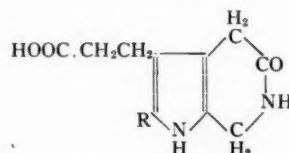
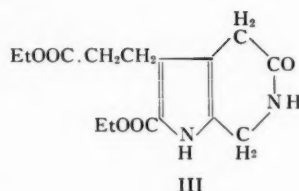
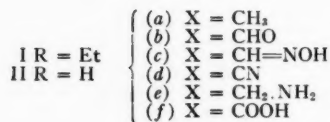
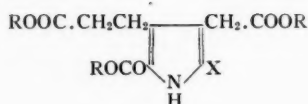
As noted in the Experimental section, our results differed from those reported by Prasad and Raper (14) in that our *Ib* and *Ic* melted higher, we obtained the lactam *III* instead of their free base *Ie*, and our *IIe* was colorless and stable, like analogous acids when these are not readily decarboxylated. The analogues of *Ie* with free acetic acid groups, *IIe*, *V*, *VIIb*, are obtained without difficulty.

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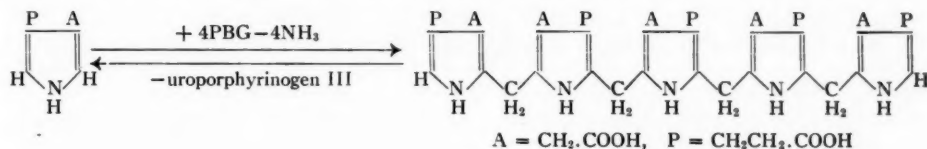


As pyrrole nitriles were assumed to be rather unreactive (4a), we attempted the preparation of II*d*, which could presumably be decarboxylated conveniently. However, not only was the nitrile group of II*d* easily reduced, but alkaline hydrolysis gave either VII*a* or II*f*. Also, the partial hydrolysis of III did not provide a shorter route to IV*b* but gave either IV*a* or VII*b*. The latter formed a hydrochloride which was also obtained by the reduction of VII*a*.

We had assumed that II*e* would be relatively difficult to decarboxylate like 2-(hydroxymethyl)-5-carboxy-pyrroles (17) or 5,5'-dicarboxy-dipyrromethanes (4c), whereas its N-acyl derivatives would decarboxylate with water at 100° like 2,3,4-tri-alkyl-5-carboxy-pyrroles (4b). Repeated unsuccessful attempts were made to prepare such acyl derivatives of II*e*, particularly the carbobenzoxy derivative, in view of the apparent instability of porphobilinogen toward acid and alkali (1). Neither could porphobilinogen be isolated after heating II*e* under various conditions, e.g., in 2 *N* hydrochloric acid, or better, in aqueous pyridine with copper acetate according to Rimington and Krol (15), although paper chromatography indicated its presence. As V gives a much more intense Ehrlich reaction than does II*e*, the quantitative course of this reaction cannot be satisfactorily followed by paper chromatography. Finally, II*e* was converted into its lactam IV*b* under conditions which had converted porphobilinogen into its lactam (1), and boiling water decarboxylated IV*b* to porphobilinogen lactam IV*c*. The identity of the latter with material of natural origin (1) was confirmed by mixed melting point, paper chromatography, infrared spectra, X-ray powder photographs, and the melting points of the derived methyl ester and keto-lactam VI (1). This last was also prepared more directly from IV*b*.

Although porphobilinogen, V, was presumably unstable in alkali (1), it was obtained from its lactam IVc with sodium hydroxide at 100°, incomplete hydrolysis giving the best yield. The removal of about 10% of unchanged lactam by repeated treatment with lead and mercuric acetates and recrystallizations (1) reduced the yield from 80 to 20%. The identity and purity of the synthetic porphobilinogen was established by paper chromatography, and by the infrared spectra and X-ray powder photographs of the natural and synthetic porphobilinogens and of their hydrochlorides. Also, the nature and amounts of the porphyrins formed indicated that the natural and synthetic porphobilinogens behaved identically in an appropriate enzyme system.

There is evidence that the biosynthesis of type III porphyrins from porphobilinogen (PBG) proceeds through uroporphyrinogen III (12, 13). As the yield of porphyrin produced enzymically from porphobilinogen is nearly quantitative (2c), the most direct routes involving analogues of known reactions (5, 6) would be through cycles involving a penta or higher polypyrane. The simplest possibilities would be expressed by³



The above pyrrole, opsopyrrole-dicarboxylic acid, is known (9), and possible dipyrromethane intermediates are being reported elsewhere.

EXPERIMENTAL

The melting points are uncorrected as taken in capillaries. The infrared spectra in Nujol mull and X-ray powder photographs are by Dr. R. N. Jones and Mr. R. Lauzon, and by Dr. Maria Przybylska. Ascending paper chromatograms were used with the upper layer of *n*-butanol – acetic acid – water (4:1:5); development was with Ehrlich's reagent. We are grateful to Professor D. Shemin for samples of natural porphobilinogen and to Professor C. Rimington, F.R.S., for samples of its hydrochloride and lactam, as well as for the comparison of the natural and synthetic porphobilinogens in an enzyme system.

2-Formyl-5-carboxy-pyrrole-3-acetic acid-4-propionic acid Triethyl Ester Oxime (Ic)

Hydroxylamine hydrochloride (2.4 g.) in 2.5 ml. of water was added to a solution of 0.82 g. of sodium in 50 ml. of ethanol, then sodium chloride was filtered off and washed with ethanol. The filtrate and washings were refluxed for 45 minutes with 10 g. of the aldehyde *Ib*,⁴ cooled, poured into 400 ml. of ice water, and left at 0°. The oxime separated, and was recrystallized from 750 ml. of 30 vol. % ethanol forming colorless needles (8.3 g., 80%), m.p. 86° (lit. 58° (14)). Ehrlich's reaction was positive after long heating. Found: C, 55.47; H, 6.33; N, 7.26%. Calc. for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.56; N, 7.61%.

2-Cyano-5-carboxy-pyrrole-3-acetic acid-4-propionic acid Triethyl Ester (Id)

The ester oxime (Ic) (10 g.) was heated with 50 ml. of acetic anhydride on the steam bath for 1 hour. After the acetic anhydride was removed *in vacuo*, the residual oil was dissolved in 250 ml. of ether. The solution was extracted twice with dilute aqueous sodium

³Dr. J. J. Scott has independently considered this hypothesis.

* We reported this aldehyde with m.p. 81° (9). Dr. Raper has informed us that Prasad and Raper found its melting point to be 78° , not 67° as they reported (14).

carbonate, dried with sodium sulphate, and the ether removed *in vacuo*. The residue, which solidified slowly at 0°, was recrystallized from ether-hexane to give the nitrile (7.2 g.) as colorless needles, m.p. 96–98°. When the mother liquor was evaporated and the residue sublimed (160°, 1×10^{-5} mm.), a further 0.7 g. of the product was obtained (total 83%). For analysis, the nitrile was recrystallized from aqueous ethanol; it then had m.p. 105–106°, Ehrlich's reaction was positive after long heating. Found: C, 58.31; H, 6.21; N, 8.16%. Calc. for $C_{17}H_{22}O_6N_2$: C, 58.27; H, 6.33; N, 8.00%.

2-Formyl-5-carboxy-pyrrole-3-acetic acid-4-propionic acid Oxime (IIc)

A solution of the ester oxime (Ic) (1 g.) and 0.5 g. of sodium hydroxide in 50 ml. of water was heated on the steam bath for 2 hours, cooled, and put through a column of Amberlite IR-120 (hydrogen form, 25 g.), eluting with water which had been boiled and cooled under nitrogen. The eluate (about 200 ml.) was evaporated at 30–35° *in vacuo* under nitrogen, and the residue dried at 20 mm. over sulphuric acid. The resulting crystalline product was extracted into acetone (Soxhlet) from which it separated as cream colored needles when pentane was added (0.68 g., 88%), m.p. 204–205° (decomp.) (lit. 201° (9), mixed m.p. 203–204°). Ehrlich's reaction was negative in the cold and red-violet on heating.

2-Aminomethyl-5-carboxy-pyrrole-3-acetic acid-4-propionic acid Triethyl Ester Hydrochloride (I (R = CH_2NH_3Cl))

(a) The ester oxime (Ic) (5 g.) in 250 ml. of ethanol and 2 ml. of concentrated hydrochloric acid was shaken with 0.5 g. of palladium black under hydrogen (1 atm.) until the latter ceased to be absorbed (about 3 hours). The catalyst was removed by filtration, and the filtrate concentrated at 30° *in vacuo*, the crystalline product being filtered off from time to time and dry ether finally being added to the mother liquors to precipitate the last of it (total 4.7 g., 89%). For analysis, the melting point was raised from 193–194° to 195–196° by recrystallizing the product from ethanol-ether; the tiny colorless needles were dried *in vacuo* at 80°. The product is soluble in warm dilute acid. Ehrlich's reaction was positive on prolonged heating. Found: C, 52.36; H, 6.90; N, 7.41; Cl, 8.97%. Calc. for $C_{17}H_{26}N_2O_6 \cdot HCl$: C, 52.23; H, 6.96; N, 7.17; Cl, 9.07%.

(b) The cyano ester (Id) (0.5 g.) in 50 ml. of ethanol and 0.25 ml. of concentrated hydrochloric acid was shaken overnight under hydrogen (60 lb./in.²) with 100 mg. of Adams' platinum oxide catalyst. After the catalyst was filtered off, the solution was concentrated *in vacuo* at 20° to about 15 ml. when crystallization began. The separation of the product was completed by adding ether to the residue and leaving the mixture at 0°. The hydrochloride (0.35 g., 63%) formed colorless tiny needles, m.p. 190–192°, mixed m.p. 192–194° with the product obtained as in (a) above.

5-Carboxy-porphobilinogen Lactam Diethyl Ester (III)

(a) The hydrochloride of the amine ester (I(R = CH_2NH_3Cl)) (2 g.) was dissolved in 30 ml. of warm ethanol, and a solution of 0.13 g. of sodium in 20 ml. of ethanol added. The solution was filtered hot, cooled, and left at 0°. The lactam (1.3 g., 82%) separated as tiny colorless needles, m.p. 228–230° (decomp.). It is insoluble in warm dilute acid. Ehrlich's reaction is faintly positive on prolonged heating. For analysis the lactam was recrystallized from aqueous ethanol and the product, m.p. 235–236° (decomp.), dried at 80° *in vacuo*. Found: C, 58.76; H, 6.57; N, 9.33; OEt, 28.92%. Calc. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09; OEt, 28.58%.

(b) The ester oxime (Ic) (5 g.) in 100 ml. of absolute ethanol and 5 ml. of ammonium hydroxide was shaken with 0.25 g. palladium black under hydrogen (50 lb./in.²) until absorption of the latter ceased (about 6 hours). The catalyst was filtered off and washed with ethanol. The filtrate and washings were concentrated *in vacuo* to about 75 ml., then diluted with 250 ml. of hot water, and left at 0°. The colorless needles (3.4 g., 81%) had the melting point of 228–231° (decomp.) raised to 233–235° (decomp.) by recrystallization from aqueous ethanol, mixed m.p. 233–234° with the product obtained as in (a) above.

5-Carboxy-porphobilinogen (IIe)

(a)⁵ The oxime (IIc) (200 mg. prepared from IIb (9)) in 10 ml. of water and 0.5 ml. of ammonium hydroxide was shaken with 50 mg. of palladium black under hydrogen (1 atm.) for 4 hours; 34 ml. of hydrogen was taken up (theory 34.2 ml.). After the catalyst was filtered off and washed with water, the product (146 mg., 77%) separated at 0° at pH 4–5. After recrystallization from dilute ammonia – acetic acid, the melting point was 233–234° (decomp.). Found in material dried *in vacuo* at room temperature: e.g., C, 48.21, 47.72; H, 5.92, 5.83; N, 10.28%. Calc. for C₁₁H₁₄N₂O₆: C, 48.89; H, 5.22; N, 10.37%; for C₁₁H₁₄N₂O₆·H₂O: C, 45.83; H, 5.60; N, 9.72%.

The result was the same when 4.5 g. was reduced (88%), or when oxime had been obtained from Ic.

(b) The lactam (III) (5 g.) was heated for ½ hour on the steam bath with 30 ml. of 2 N sodium hydroxide and 20 ml. of ethanol. After the solution was cooled and filtered, the product was isolated as under (a) above, giving 3.8 g. (87%), m.p. 225–230°, raised to about 233° (decomp.) by recrystallization. It was dried *in vacuo* at 25° and then exposed to the air. Found: C, 46.35, 46.42; H, 5.70, 5.55; N, 9.88%.

(c) The hydrochloride of the amine ester (I(R = CH₂NH₃Cl)) (3.2 g.) in 20 ml. of 2 N sodium hydroxide was heated in the steam bath for ½ hour beyond the time required for its complete dissolution. The product (2.01 g., 90%) was isolated as under (a) above. Recrystallization raised the melting point from 220–225° to 230–233° (decomp.).

All these products formed stable colorless needles, *R_f* 0.38. Ehrlich's reaction was slowly positive in the cold. Regardless of the method of preparation the infrared spectra and X-ray powder photographs of dried samples showed some identities but usually varied within limits. However, the X-ray powder photographs were identical when the crystals were kept wet. This compound had previously been described as rapidly turning red (14).

5-Carboxy-porphobilinogen Lactam (IVb)

5-Carboxy-porphobilinogen (IIe) (10 g.) in 100 ml. of pyridine and 300 ml. of water was treated dropwise with ammonium hydroxide until solution was complete. The solution was cooled in ice, 50 ml. of acetic acid added, and 50 ml. of acetic anhydride added dropwise to the clear solution, with stirring, at 0–5° over 40 minutes. After a further hour at 0°, the slightly yellowish microcrystalline product was centrifuged off and washed successively with water, acetone, and ether. More was obtained by concentrating the mother liquor *in vacuo* at 25–30° in a Craig-type rotary evaporator, the total being 5.25 g. (56%). It was recrystallized for analysis by dissolving in warm N ammonium hydroxide, adjusting the pH to 4–5 with N acetic acid and allowing the solution to cool slowly, finally to 0°. It formed colorless hexagonal plates, decomposing above 325°.

⁵This was carried out by Dr. D. M. MacDonald (Ref. 9).

slowly turning yellowish in air. Ehrlich's reaction was weak in the cold but strong on heating, R_f 0.58. Found: C, 52.10; H, 4.65; N, 11.00%. Calc. for $C_{11}H_{12}O_5N_2$: C, 52.38; H, 4.80; N, 11.11%.

Porphobilinogen Lactam (IVc)

5-Carboxy-porphobilinogen lactam (IVb) (5 g.) was completely extracted from a Soxhlet thimble into 250 ml. of boiling water under nitrogen. The suspension was cooled to 0° under nitrogen and the product filtered off. More was obtained by concentrating the mother liquors under nitrogen. It then formed colorless rhomboidal plates, becoming yellowish in air (3.32 g., 80%), R_f 0.78. Ehrlich's reaction was strongly positive in the cold, m.p. 280–283° (decomp.). After recrystallization from boiling water under nitrogen (for analysis), the product had m.p. 282–284° (decomp.). It was dried at 80° and 1×10^{-5} mm. Found: C, 57.55; H, 5.80; N, 13.19%. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46%.

The fluorescence appears to be due to a small amount of impurity (perhaps the pyridone) running slightly behind the Ehrlich-positive spot on paper chromatography.

Porphobilinogen Lactam Methyl Ester

In agreement with the results reported by Cookson and Rimington (1), this formed colorless needles, m.p. 248–250°, when prepared from synthetic porphobilinogen lactam (IVc) in 60% yield by their method. Ehrlich's reaction was positive in the cold. Found: C, 59.29; H, 6.17; N, 12.73%. Calc. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.34; N, 12.60%.

Porphobilinogen Keto-lactam (VI)

(a) This was prepared from the synthetic porphobilinogen lactam (IV(R = H)) in 50% yield according to Cookson and Rimington (1). It formed colorless prisms which darkened and decomposed above 325°.

(b) 5-Carboxy-porphobilinogen lactam (IVb) (35 mg.) in 2 g. of polyphosphoric acid was slowly heated to 80–90°. After carbon dioxide ceased to be evolved, the temperature was slowly raised to 110° and held at 110–115° for 10 minutes. The solution was cooled, diluted with 20 ml. of water, and kept 1 hour at 0°. The product was filtered off, washed, and recrystallized from boiling water, giving colorless plates (13 mg., 50%) decomposing above 325°. Ehrlich's reaction was negative hot. The product was dried at 100° *in vacuo*. Found: C, 63.09; H, 5.43; N, 14.81%. Calc. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73%.

In Nujol mull, the infrared spectra of the products prepared according to (a) and (b) were identical.

Porphobilinogen (V)

The synthetic porphobilinogen lactam (IVc) (500 mg.) in 3 ml. of 2 *N* sodium hydroxide was heated on the steam bath under nitrogen for 40 minutes.⁶ After the solution was cooled under nitrogen, diluted to 50 ml. with water, and brought to pH 4–5 with acetic acid, excess 10% lead acetate was added and the precipitate filtered off, washing with 1% lead acetate. The colorless filtrate and washings were treated with a slight excess of 15% mercuric acetate, and the yellowish white precipitate centrifuged off and washed with 1% mercuric acetate. The mercury precipitate was diluted to 15 ml. with water and decomposed by hydrogen sulphide. Mercuric sulphide was removed by centrifuging, then filtering, washing it with 2×10 ml. of water. The filtrate and washings were freeze-

⁶Porphobilinogen may be precipitated in about 80% yield at this stage but paper chromatography then shows it to contain about 10% of the lactam.

dried, the slightly pink residue dissolved in a little *N* ammonium hydroxide, the pH adjusted to 4-5 with acetic acid, and the solution cooled in ice and salt. Porphobilinogen crystallized slowly (about 200 mg., 35%) as a slightly pink microcrystalline powder, m.p. 170-174° (decomp.). Ehrlich's reaction was strongly positive in the cold, R_f 0.49-0.50. This product usually still contained traces of the lactam, which were removed by a repetition of the lead and mercury treatments, giving a product of melting point 172-175° (decomp.) in a yield reduced to about 20%. For analysis, it was dried at 25° in a high vacuum, then exposed to air. Found: C, 49.15, 49.29; H, 6.56, 6.63; N, 11.23%. Calc. for $C_{10}H_{14}O_4N_2 \cdot H_2O$: C, 49.17; H, 6.60; N, 11.47%.

Like the natural product (1), it is converted to uroporphyrins by hot dilute hydrochloric acid (10). The infrared spectrum of porphobilinogen is not nearly as characteristic as those of its hydrochloride and lactam.

Porphobilinogen Hydrochloride

The synthetic porphobilinogen was converted into its hydrochloride according to Cookson and Rimington (1). Found: C, 43.37; H, 6.52; N, 9.77%. Calc. for $C_{10}H_{14}N_2O_4 \cdot HCl \cdot H_2O$: C, 42.78; H, 6.10; N, 9.98%.

The natural and the synthetic porphobilinogen hydrochlorides (3 mg.) were converted to porphyrins by a blood hemolyzate (2a), the porphyrins separated and estimated (2b) and their type purity established by paper chromatography with lutidine (3). Only the following resulted (the respective amounts in μ g.): uroporphyrin III together with "pseudo-uroporphyrin" (436 and 444), coproporphyrin III (140 and 130), protoporphyrin (13 and 10).

2,5-Dicarboxy-pyrrole-3-acetic acid-4-propionic acid (IIf)

The cyano ester (Id) (2.5 g.) was heated on the steam bath with 25 ml. of 10% sodium hydroxide for 2 hours under nitrogen. The cooled solution was deionized in a column of Amberlite IR-120 (100 g., hydrogen form), eluting with about 400 ml. of water which had been boiled and cooled under nitrogen. The eluate was evaporated at 25-30° *in vacuo* under nitrogen, and the slightly pink crystalline residue was recrystallized from a little hot water. The product (1.30 g., 64%) separated as colorless needles, darkening above 200° and decomposing at about 230°. Ehrlich's reaction was very weak in the cold but stronger on heating. There was no trace of a CN band in its infrared spectrum. Found: C, 46.58, 46.39; H, 3.98, 3.73%. Calc. for $C_{11}H_{11}O_8N$: C, 46.32; H, 3.89%.

2-Cyano-5-carbethoxy-pyrrole-3-acetic acid-4-propionic acid (VIIa)

The cyano ester (Id) (300 mg.) in 5 ml. of ethanol and 2.0 ml. of *N* sodium hydroxide was heated for $\frac{1}{2}$ hour on the steam bath. After the ethanol was removed by passing nitrogen through the heated solution, the slightly yellowish crystalline product (160 mg., 63%) was precipitated with sulphur dioxide at 0°, filtered off, and washed with ice water. For analysis it was recrystallized three times by extracting into ether (Soxhlet) and precipitating with hexane; it was then dried at 80° *in vacuo*. It formed tiny colorless needles, m.p. 172-174° (decomp.). Ehrlich's reaction was slowly positive on prolonged heating. Found: C, 52.38; H, 5.03; N, 8.98%. Calc. for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80; N, 9.52%.

5-Carbethoxy-porphobilinogen Lactam (IVa)

The lactam (III) (600 mg.) was heated for 20 minutes on the steam bath with 10 ml. of ethanol and 2.1 ml. of *N* sodium hydroxide in an open flask. The cooled solution was

diluted to 20 ml. with water, brought to pH 4-5 with acetic acid, and left 1 hour at 0°. The fine precipitate was centrifuged off, dried at 1×10^{-5} mm., and crystallized from dry acetone (Soxhlet). The product (320 mg., 60%) formed tiny colorless needles, m.p. 260-265° (decomp.), raised to 264-267° by two similar recrystallizations. Ehrlich's reaction was slowly positive on heating. It was dried at 80° *in vacuo*. Found: C, 55.76; H, 5.70; N, 10.09%. Calc. for $C_{13}H_{16}O_5N_2$: C, 55.71; H, 5.75; N, 10.00%.

5-Carbethoxy-porphobilinogen (VIIb)

The lactam (III) (300 mg.) in 5 ml. of ethanol was heated on the steam bath, 2.1 ml. of *N* sodium hydroxide added, and the heating continued for $\frac{1}{2}$ hour. Ethanol was removed by passing a stream of nitrogen through the hot solution. The solution was cooled, diluted to 10 ml. with water, the pH brought to 4-5 with acetic acid, and the solution left at 0° for 2 hours. The product (160 mg., 55%) formed colorless needles, m.p. 260-265° (decomp.). Ehrlich's reaction was positive on heating. For analysis the product was recrystallized from *N* ammonium hydroxide by adding *N* acetic acid and dried at 80° *in vacuo*. Found: C, 52.10; H, 6.08; N, 9.36%. Calc. for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39%.

5-Carbethoxy-porphobilinogen Hydrochloride (VII (R = CH₂NH₃Cl))

(a) The above base (VIIb) was dissolved in warm ammonium hydroxide, and a slight excess of 2 *N* hydrochloric acid added. The product separated as colorless needles, m.p. 234-236° (decomp.), mixed m.p. 234-237° (decomp.) with the same product obtained as under (b).

(b) The nitrile (VIIa) (250 mg.) in 25 ml. of water and 0.5 ml. of concentrated hydrochloric acid was shaken with 0.15 g. of Adams' platinum oxide under hydrogen (50 lb./in.²) for 4 hours. After filtration, the solution was evaporated to dryness *in vacuo* at 25-30° under nitrogen. The faintly pink solid residue was recrystallized from alcohol-ether giving colorless needles (180 mg., 63%) darkening above 160°, m.p. 233-236° (decomp.). Ehrlich's reaction was negative cold, positive hot. For analysis the melting point was raised to 235-237° by recrystallizing twice from alcohol-ether, and the product was dried at 80° *in vacuo*. Found: C, 46.42; H, 5.61; N, 8.19%. Calc. for $C_{13}H_{18}N_2O_6 \cdot HCl$: C, 46.65; H, 5.72; N, 8.37%.

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THE PHOTOINITIATED ADDITION OF MERCAPTANS TO OLEFINS

III. THE KINETICS OF THE ADDITION OF THIOPHENOL TO STYRENE AND TO 1-OCTENE¹

R. H. PALLER AND C. SIVERTZ

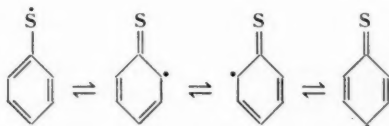
ABSTRACT

Kinetic studies were made of the free radical photoinitiated addition of thiophenol to 1-octene and to styrene in the absence of oxygen. In addition to the usual attack, chain transfer, and termination steps, it is found that a reverse reaction accompanies the attack step, $\phi\dot{S} + M \rightleftharpoons \dot{C}$. The rate constants for the thiophenol-styrene reaction were calculated to be $k_p \approx 2 \times 10^3$, $k_{tr}^S = 3 \times 10^3$, $k_t = 2 \times 10^7$ liters.moles⁻¹sec.⁻¹. The over-all activation energies for the two reactions were found to be $E(1\text{-octene}) = 1.2$ kcal., $E(\text{styrene}) = 2.4$ kcal.; suggestions are submitted as to why these activation energies are so low. These reactions are compared with *n*-butyl mercaptan-olefin reactions.

INTRODUCTION

Past studies in this laboratory (1, 6) were concerned with the kinetics of the free radical photoinitiated addition of *n*-butyl mercaptan to unconjugated and conjugated double bonds (i.e. 1-pentene and styrene).

The work described in this paper was begun with the object of investigating what the effect would be when the unconjugated mercaptan (butyl mercaptan) was replaced by a conjugated mercaptan (thiophenol). The attacking thiyl radical would now be resonance stabilized.



Because of this, several consequences were anticipated: (a) the attack step should be considerably weaker, (b) the mercaptyl hydrogen would be more labile, (c) the termination coefficient of radicals should be reduced. These effects were investigated and are discussed in the light of the mechanism proposed.

It was observed that some reaction (free radical in nature) occurred in the dark when oxygen was present. Moreover, it is likely that this system also reacts by a normal Markovnikov addition though slowly under the conditions of the present study. Owing to the general sensitivity of the reaction to these various mechanisms and the tediousness of transferring the thiol under vacuum, certain obvious extensions of this work have not been pursued; nevertheless the principal characteristics in relation to the molecular kinetics have been established.

METHODS

The reactions were initiated photochemically and the rate of reaction was followed dilatometrically. The apparatus used was described by Onyschuk and Sivertz (6). The rate constant for recombination of radicals (k_t) is related to the half-life (λ) and rate of initiation ($k(I)$) as follows:

$$[1] \quad k_t = 1/\lambda^2 k(I).$$

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Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

λ was determined by the sector method and the method of evaluating $k(I)$ will be described later. In previous work an independent initiator was used, i.e. azo-bis-isobutyronitrile (AIN). It was found that AIN and thiophenol both undergo photochemical decomposition in the same region of the ultraviolet spectrum; therefore, it was not useful to use AIN in this case. Instead, the reactions were initiated solely through thiophenol. It was also found that oxygen can account for some initiation. In order to exclude molecular oxygen from the reaction, an apparatus for degassing and handling three-component systems was developed. The apparatus consists of three pairs of traps connected through a manifold tube to the dilatometer reaction cell, Fig. 1. The reagents

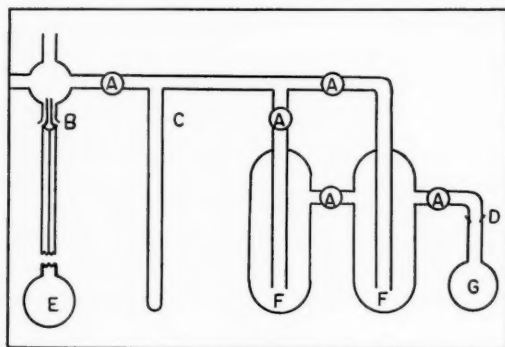


FIG. 1. Typical degassing unit.

- | | |
|------------------------------|-----------------------------|
| A—stopcocks | E—dilatometer reaction cell |
| B—ground glass through-joint | F—cold finger traps |
| C—calibrated tube | G—reservoir |
| D—ground glass joint | |

were degassed by trap-to-trap distillation while the system was being pumped out. The traps were cooled with a dry ice-acetone mixture and, therefore, any oxygen in the reagents passed out of the system through the pump. The degassed reagents were measured in calibrated tubes, *C*, and then transferred to the dilatometer reaction cell, *E*, which was sealed off when filled to the desired mark, and the reaction initiated and followed as previously reported (6).

In order to test the effectiveness of this apparatus for the removal of oxygen, the termination constant for vinyl acetate radicals was determined at 25° C. The reasons for choosing this reaction are: (a) it is very sensitive to small amounts of oxygen and (b) Bartlett (2) and Matheson (4) have done excellent work in establishing the termination constant. The reagents were degassed in the apparatus described above; other techniques were those used by Bartlett and Matheson. The rate of initiation, induced through AIN, was determined by duroquinone inhibition, and by comparison with a thermally initiated reaction (see determination of $k(I)$). The half-life of the radicals was determined by the sector method (5). This procedure yielded values for the termination constant of 5.4×10^7 and 8.3×10^7 liters.moles⁻¹sec.⁻¹ respectively for the two different methods of determining $k(I)$. The results are in satisfactory agreement with those of P. D. Bartlett (5.88×10^7 liters.moles⁻¹sec.⁻¹). Hence it was concluded that the procedure is efficient in removing oxygen from liquid reagents. This apparatus was used for the experiments described in the remainder of this paper.

EXPERIMENTAL AND RESULTS

Materials

Vinyl acetate.—Polymer Corporation Ltd. reagent was distilled under nitrogen through a 100-cm. Todd column packed with glass helices. The middle fraction was retained, b.p. (745.7 mm. Hg) 71.5° C. This was stored in a bottle at 4° C.

Benzene.—Merck reagent grade, thiophene free, was used without any purification other than degassing.

Duroquinone.—Merck reagent grade was used without any further purification, m.p. 111–112° C.

Thiophenol.—Evans Chemetics reagent was purified as described by Harrison (3).

1-Octene.—Phillips Petroleum Co. Pure Grade was used without any purification other than degassing.

Styrene.—Polymer Corporation Ltd. was distilled through a 40-cm. Vigreux column to remove the inhibitor present. The middle fraction was retained, b.p. (10 mm. Hg) 37–39° C.

Azo-bis-isobutyronitrile (AIN).—This was prepared by the method of Overberger *et al.* (8), m.p. 102.5–103.5° C.

The concentrations of reagents used in the following experiments are shown in Table I.

TABLE I
CONCENTRATIONS* OF REAGENTS USED

Reagents†	Series		
	I	II	III
AIN	0.15		
Thiophenol	0.86	0.86	0.86
1-Octene			1.12
Styrene	1.56	1.56	

*All concentrations are in moles per liter.

†Benzene was used as solvent except where otherwise specified.

Determination of the Rate of Initiation ($k(I)$)

In order to determine the rate at which radicals entered the system by photolysis of the thiol at 25° C., the reaction was studied at 50° C. with initiation produced by (a) the thermolysis of AIN and no illumination, $k(I)_T$ (concentrations as in series I), and (b) the photolysis of the thiol and no AIN, $k(I)_p$ (concentrations as in series II), Fig. 3. From (a) we deduce the initiation, $k(I)_T$, from the well-known kinetics for AIN thermolysis (10). By comparing rate (a) with rate (b), $k(I)_p$ may then be calculated from the steady state conditions:

$$[2] \quad [R_a/R_b]^2 = k(I)_T/k(I)_p.$$

It had been established that this reaction obeys the usual root law for free radical reactions. By this procedure $k(I)_p$ was found to be 8.5×10^{-7} moles.liters⁻¹sec.⁻¹ at 50° C. It is assumed that the temperature coefficient of photolysis is negligible and hence this may be taken as $k(I)_p$ at 25° C.

Determination of the Rate of Termination (k_t) (Thiophenol-Styrene)

Fig. 2 shows the variation of the rate of reaction with sector speed. The mean half-life of the active species was derived from these data by comparison with the theoretical curve for intermittent illumination with a light to dark period ratio of 1:3 (5). In spite of the scatter of points about the theoretical curve it may be concluded that the half-life

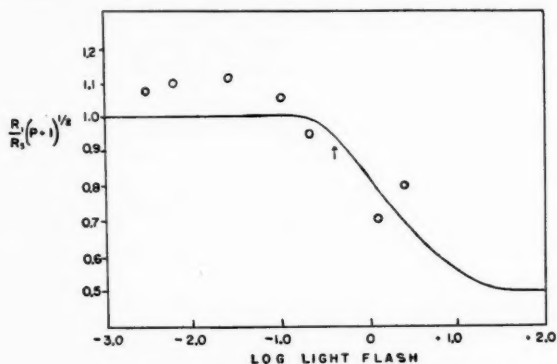


FIG. 2. Sectored rates of thiophenol-styrene reaction.
 R_i —rate with intermittent illumination.
 R_s —rate with steady illumination.
 P —ratio of dark period to light period (3:1).

lies between 0.4 to 0.2 seconds, with a consequent value for the termination constant, from equation [1] and the measured $k(1)$, of $ca. 1 \times 10^7$ liters.moles⁻¹sec.⁻¹. It was not practical to attempt a determination of the k_t for the thiophenol-1-octene reaction because it was so slow.

Over-all Rates of Reaction

The reaction rates were followed dilatometrically by means of a cathetometer and recorded as centimeters of contraction per minute. A series of reactions was carried to different degrees of contraction and the remaining concentration of thiophenol was analyzed for with a Fisher Coulomatic Titrimeter. In this way the relation between height and molarity, $\mu H = M$, was established. The thiophenol-styrene reaction had an initial rate of 8.3×10^{-5} moles.liters⁻¹sec.⁻¹ while that of the 1-octene-thiophenol was 2.2×10^{-5} moles.liters⁻¹sec.⁻¹. Typical reaction curves are shown in Fig. 4.

Activation Energy

These were determined using the Arrhenius plot of $\ln(\text{rate}/T)$ vs. $1/T$. The activation energy for the thiophenol-styrene reaction was 2.4 kcal. (Fig. 5) using benzene as solvent and 6.3 kcal. (Fig. 5) in cyclohexane. For the thiophenol-1-octene reaction the activation energy was found to be 1.2 kcal. in benzene (Fig. 5).

OTHER RELEVANT DATA

cis-trans Conversion

Recent experiments in this laboratory (11) have shown that in a similar reaction of thiophenol with either of the pure isomers of 2-butene, both the *cis* and the *trans* isomers are present after a short period of reaction. This conversion could only be possible as a result of the reversible dissociation of the composite radical (ϕSM).

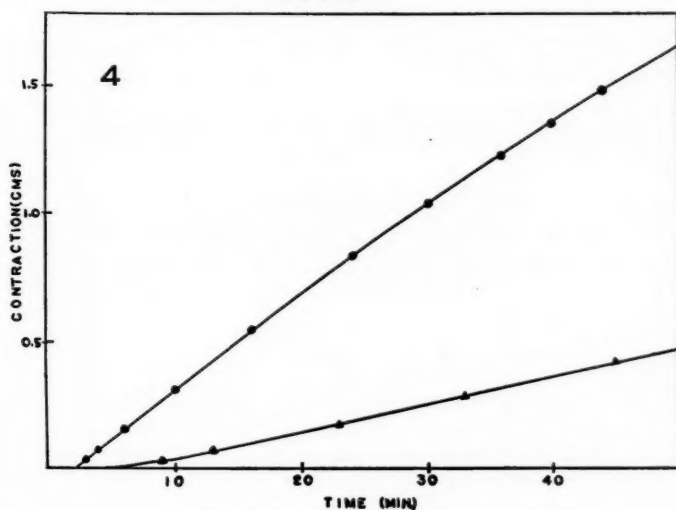
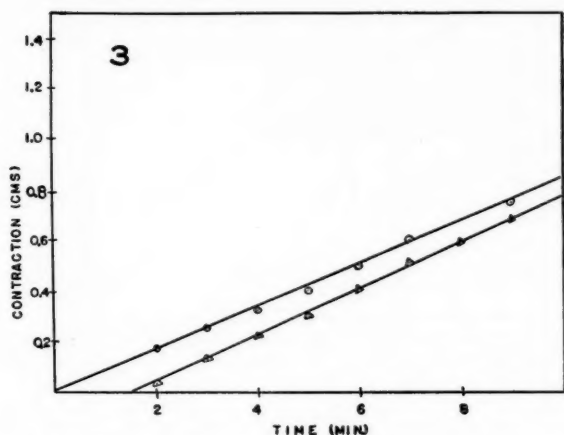


FIG. 3. Determination of $k(I)$.
 O—Rate initiated by thermolysis of AIN.
 Δ—Rate initiated by photolysis of thiophenol.

FIG. 4. Typical reaction rate curves.
 ●—Thiophenol-styrene.
 ▲—Thiophenol-1-octene.

Rate Dependence on Concentration

Onyschuk (7) showed that the thiophenol-1-octene reaction is first order dependent on both monomer and mercaptan (Fig. 6), and also that the thiophenol-styrene reaction is first order in mercaptan (Fig. 7a). These authors have found that the latter reaction is monomer dependent at small concentrations and very rapidly becomes independent of monomer concentration except for a gradual rise in rate with monomer concentration which is due to the propagation reaction growing in importance (Fig. 7b).

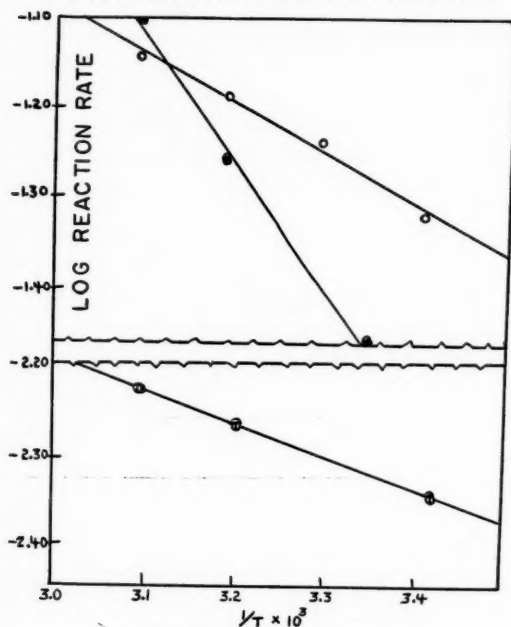
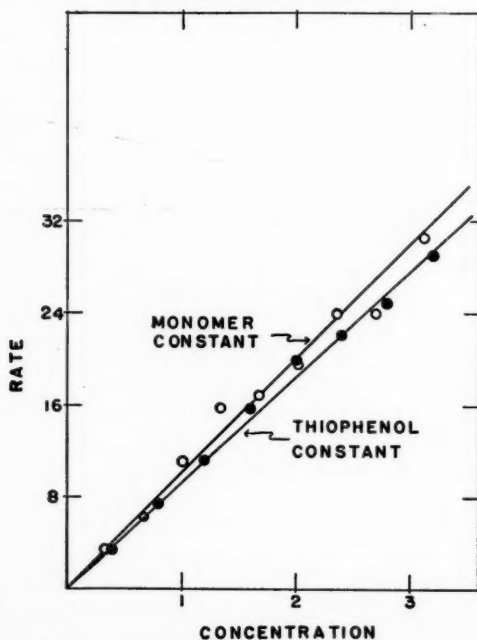


FIG. 5. Activation energies.

- Thiophenol-styrene in benzene.
- Thiophenol-styrene in cyclohexane.
- ⊙—Thiophenol-1-octene in benzene.

FIG. 6. Rate dependence on concentration (thiophenol-1-octene reaction) (rates in moles.liters⁻¹sec.⁻¹, concentrations in moles.liters⁻¹).

- Varying thiophenol.
- Varying 1-octene.

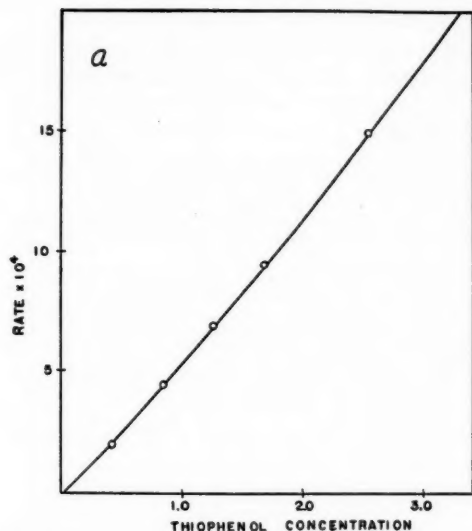


FIG. 7a. Rate dependence on thiophenol concentration (thiophenol-styrene reaction) (rates in moles.liters⁻¹sec.⁻¹, concentrations in moles.liter⁻¹).

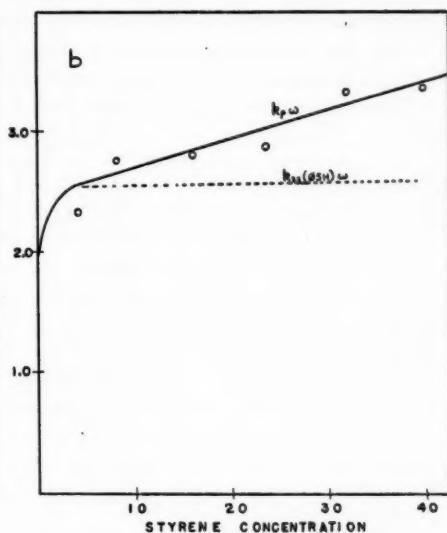
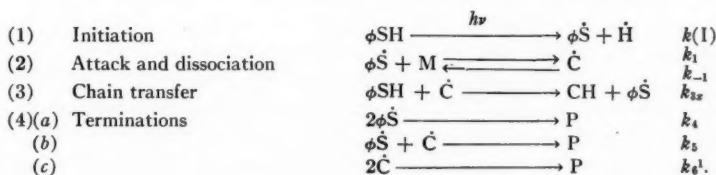


FIG. 7b. Rate dependence on styrene concentration (thiophenol-styrene reaction) (rates in moles.liters⁻¹sec.⁻¹, concentrations in moles.liter⁻¹).

DISCUSSION

On the basis of the above data we conclude that the mechanism proposed for gas phase studies in this laboratory (9) applies also to the thiophenol-olefin reactions in the liquid phase. The basic steps of this mechanism are:



The elementary reactions and terminology are explained fully by Sivertz *et al.* (6). As discussed by these authors, propagation of the composite (\dot{C}) radical into monomer can be neglected in the case of 1-octene but not in the case of styrene. Radical \dot{C} is concluded to be a very weak intermediate radical, in the case of 1-octene, which can readily dissociate into reactants or capture the labile hydrogen of the mercaptan. The composite radical involving styrene will be more stable. The rate expression developed from steady state kinetics is as follows:

$$[3] \quad R = [k_{3x}(\phi SH) + k_p(M)]\omega / \left(1 + \frac{\mu k_{3x}(\phi SH) + \mu k_{-1}}{k_1(M)}\right).$$

The second term in the numerator, i.e. $k_p(M)$, applies only in the case of styrene; $\omega = k(I)/(k_t)^{1/2}$, $\mu = (k_t^{\phi \dot{S}}/k_t^{\dot{C}})^{1/2}$, and the concentrations are expressed in moles per liter.

Thiophenol-1-Octene Reaction

The low activation energy found for the thiophenol-1-octene reaction could be accounted for in the following ways. From equation [5] below, the expression for the over-all activation energy is seen to be

$$[4] \quad E_{\text{over-all}} = E_{3z} + \Delta H - \frac{1}{2}E_t,$$

where ΔH is the change in enthalpy for the formation of the composite radical, which has a negative value. The relatively small value of $E_0 = 1.2$ kcal. compared to *ca.* 3.0 kcal. for butyl mercaptan can then be due to this small negative enthalpy change and quite likely to some activation energy in the termination step.

This reaction may also be viewed as a third-order reaction involving a favorable collision between $\phi\dot{S}$, M, and ϕSH , in which the composite radical is first formed but short-lived in the case of 1-octene and long-lived in the case of styrene. The classical reaction between NO and O_2 is similar to the octene reaction proceeding, as it does, through a complex $NO \cdot O_2$. The question of whether to describe such reactions as true third-order or consecutive reactions is meaningless without some convention which defines the limits of time spent in "normal collisions" of this type.

Comparison of Thiophenol Octene with Thiophenol Styrene Reaction

The rate of reaction of thiophenol-1-octene is slower than that of thiophenol-styrene. This is the reverse of what is found for these same monomers reacting with *n*-butyl mercaptan. An examination of the rate expressions for these two reactions leads to an understanding of why this could be so. The rate of the thiophenol-1-octene reaction was shown to be first order in *both* monomer and mercaptan. This result is possible only if in equation [3] $\mu k_{-1}/k_1(M) > \mu k_{3z}(\phi SH)/k_1(M) > 1$, which reduces the equation to:

$$[5] \quad \begin{aligned} R_I &= k_{3z}^0 (\phi SH) [k_1(M)/\mu k_{-1}] \omega^I, \\ [5a] \quad &= k_{3z}^0 (\phi SH) [K(M)/\mu] \omega^I. \end{aligned}$$

On the other hand, in the case of the thiophenol-styrene reaction we may anticipate that the terms in the denominator in equation [3] are negligible compared to unity. The following reasons are submitted: (a) the composite radical is relatively stable, hence the transfer rate is low, (b) because of this resonance stabilization the dissociation of the composite radical is low, and (c) the attack of the thiophenyl radical on styrene is much more rapid than the transfer, as in the case of butyl mercaptan - styrene (3). These expectations are seen to be justified on analysis of Fig. 7b. Equation [3] may then be written as:

$$[6] \quad R_{II} = [k_{3z}^s (\phi SH) + k_p(M)] \omega^{II}.$$

We now proceed to consider reasons for the observed relative magnitudes of R_I and R_{II} . If, as seems probable, ω^I and ω^{II} are nearly equal, and since R_I is less than R_{II} , in spite of the fact that k_{3z}^0 must be greater than k_{3z}^s , the relative rates must have their origin in the magnitude of the equilibrium constant, K , which is involved in the thiophenol-octene reaction only. K is defined as

$$[7] \quad K = k_1/k_{-1} = [\phi SM]/[\phi\dot{S}][M].$$

It has been noted above that equation [5a] is consistent with the established order of the thiophenol-octene reaction; we may now conclude further that K must indeed be less than unity in order to account for the experimental fact that $R_I < R_{II}$. A low value

of K is also consistent with the relative resonance stabilization of the radicals $\phi\dot{S}M$ and $\phi\dot{S}$.

Equation [6] shows that when there is no propagation, the reaction rate reaches a limiting rate, $k_{3z}^s(\phi SH)\omega$. This rate was obtained from the plot shown in Fig. 7b as 2.5×10^{-4} moles.liters⁻¹sec.⁻¹. The value of $(k(1)/k_t)^{1/2}$ for these reactions was 9.6×10^{-3} moles.liters⁻¹ and hence k_{3z}^s was calculated to be ca. 3×10^3 liters.moles⁻¹sec.⁻¹.*

The magnitude of the rate constant for propagation, k_p , was estimated from the slope of the plot in Fig. 7b. The slope has the value of $k_p\omega$ of 2×10^{-5} sec.⁻¹; therefore k_p has the value ca. 2×10^2 liters.moles⁻¹sec.⁻¹. When monomer concentration is expressed in terms of mercaptan concentration and like terms in the rate expression collected, the term in brackets in equation [6] becomes $[(k_{3z}^s + k_p)(\phi SH) + k_p A]$, in which $k_p A\omega$ is found to contribute only 5% of the total rate. Hence, if the effective extinction coefficient for mercaptan is small, then ω can be written as: $\omega'(\phi SH)^{1/2}$. A good approximation to the rate expression then should be:

$$[8] \quad R = (k_{3z}^s + k_p)(\phi SH)^{3/2}\omega'$$

When the rate is expressed in disappearance of mercaptan, the integrated form of this equation implies that a plot of $1/(\phi SH)^{1/2}$ vs. t is a straight line with a slope of $(k_{3z}^s + k_p)/2$. Such a plot is shown in Fig. 8, the slope of which gives ca. 3×10^3 for the value of

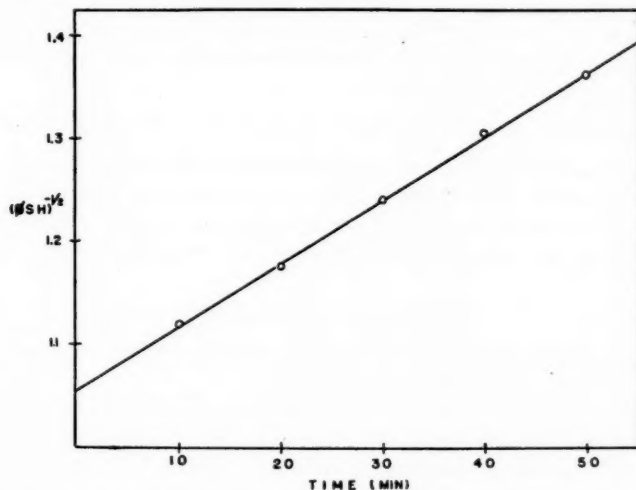


FIG. 8. Evaluation of $(k_p + k_{3z}^s)$ from approximate rate expression (concentration of thiophenol in moles.liter⁻¹).

$(k_{3z}^s + k_p)$. This is in satisfactory agreement with the values for these rate constants given above and therefore the assumptions made above appear to be valid. In a parallel study, in this laboratory, of the system, *n*-butyl mercaptan - styrene, A. Harrison (3) found the attack constant, k_1 , for *n*-butyl thiyl radical on styrene to be $6 \times 10^{+3}$ liters.moles⁻¹sec.⁻¹ and $k_{3z}^s = 1.2 \times 10^3$ liters.moles⁻¹sec.⁻¹, and hence the ratio $\mu k_{3z}^s/k_1$ is

*A similar example, studied in this laboratory, is the case of the cyclohexene - *n*-butyl mercaptan reaction which has no propagation and a low rate constant for chain transfer. This reaction rate is monomer dependent only at very low concentrations of monomer and very quickly reaches a limiting rate (3).

exceedingly small. While we have not measured the corresponding attack constant, k_1 , for the thiophenol, the shape of the curve, reaction rate vs. monomer in Fig. 7a, assures us that this ratio for the thiophenol-styrene system should also be entirely negligible compared to the unity except at very low monomer concentrations. Hence the rate expression given in equation [6] is valid.

With regard to the k_p value, A. Harrison (3) has found this to have a value of 230 for *n*-butyl mercaptan-styrene. We estimate k_p to be 200 for thiophenol-styrene (Fig. 7b). This result implies that the two composite radicals are about equivalent in their ability to attack the same conjugated monomer. However, if these composite radicals are in fact equivalent we should expect a much larger difference in the rates k_{3z}^s with butyl mercaptan and with thiophenol.

Preliminary experiments in this laboratory indicate that the sulphhydryl hydrogen of thiophenol is several hundred times more labile, in terms of diphenyl picryl hydrazyl, than that of *n*-butyl mercaptan. Hence we would expect that k_{3z}^s for the thiophenol reaction might be greater than k_{3z}^s for the *n*-butyl mercaptan. The ratio found however is only ca. 1:3, which reflects the greater stabilization of the composite radical of the thiophenol-styrene system.

The thiophenyl radical, the composite radical, and the styryl radical are all resonance stabilized; therefore any possible radical recombination involves stabilized radicals and hence a low termination constant should be expected. It was not surprising, therefore, to obtain a value as low as 2×10^7 liters.moles⁻¹sec.⁻¹. Moreover it is possible to estimate the ratio of $\phi\dot{S}$ to \dot{C} radical steady state concentrations as follows. The steady state equation for the composite radical, \dot{C} , is:

$$[9] \quad k_1(\phi\dot{S})(M) = k_{-1}(\dot{C}) + k_p(M)(\dot{C}) + k_{3z}^s(\dot{C})(\phi SH) + \text{terminations.}$$

It seems highly probable that in the case of styrene $k_{-1}(\dot{C})$ is less than the transfer rate. Also it has been shown that $k_p(M)$ is about 5% of this rate. Finally, since the kinetic chain length was found to be ca. 1000, terminations are entirely negligible compared to transfer, and hence the ratio of thiophenol radical to composite radical can be expressed as:

$$[10] \quad [\phi\dot{S}]/[\dot{C}] \simeq k_{3z}^s(\phi SH)/k_1(M).$$

Since the magnitude of k_1 is many times greater than k_{3z}^s the termination rate constant is most likely that for the composite radicals.

The low activation energy of 2.4 kcal. for this reaction should be compared with 5.8 kcal. for the *n*-butyl mercaptan-styrene reaction (3). This activation energy is for the reaction as expressed in equation [6]. The low value is to be expected for a reaction with a transfer step, which involves a very labile hydrogen as a rate-determining step. In addition some considerable activation energy may be involved in termination since k_t was found to have a relatively low value.

The value of 6.3 kcal. for the same reaction in cyclohexane as solvent is as yet unexplained. It has been suggested that this could be due to a transfer reaction involving the solvent; however, this is very unlikely with thiophenol present, in which the sulphhydryl hydrogen is many thousand times more labile than hydrogen on cyclohexane.

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NOTES

INTERNAL ROTATION X. THE RAMAN SPECTRUM OF LIQUID 1-CHLORO-2-BROMOETHANE-1,1- d_2 ¹

J. K. WILMSHURST² AND H. J. BERNSTEIN

The Raman spectrum of $\text{ClCD}_2\text{CH}_2\text{Br}$ has been obtained photoelectrically with a White Raman spectrometer (7) and depolarization ratios measured by the method of Edsall and Wilson (3). An assignment of all the fundamentals in the *trans* and *gauche* forms, with the exception of the torsional modes, has been made by analogy with the undeuterated molecule (2) and is given in Table I.

The *trans* form of $\text{ClCD}_2\text{CH}_2\text{Br}$ has only one plane of symmetry and there should be

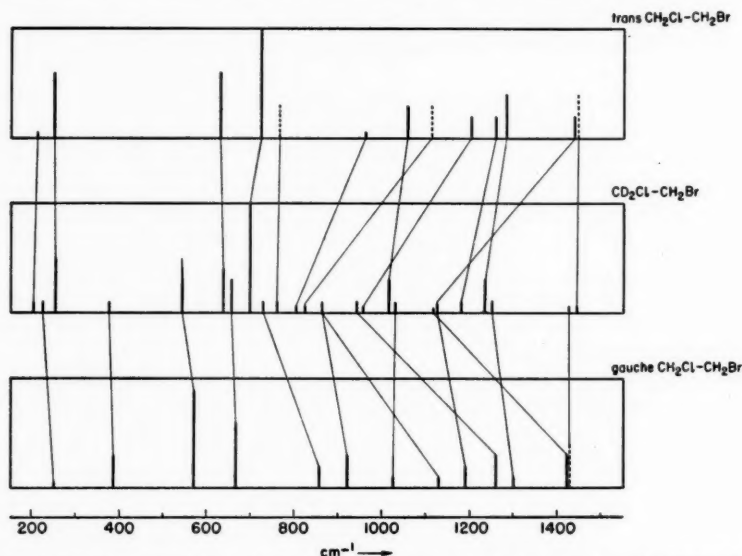


FIG. 1. A line diagram relating the fundamental frequencies in *trans* and *gauche* $\text{ClCH}_2\text{CH}_2\text{Br}$ with the observed frequencies in $\text{ClCD}_2\text{CH}_2\text{Br}$.

Upper field: *trans* $\text{ClCH}_2\text{CH}_2\text{Br}$
 Center field: $\text{ClCD}_2\text{CH}_2\text{Br}$ (only bands assigned as fundamentals are shown)
 Lower field: *gauche* $\text{ClCH}_2\text{CH}_2\text{Br}$

11 modes symmetrical with respect to this plane and, therefore, polarized and seven modes antisymmetrical with respect to the plane and, therefore, depolarized. The *gauche* form of $\text{ClCD}_2\text{CH}_2\text{Br}$ has the identity operation as its only element of symmetry and hence all 18 vibrational modes should be polarized.

The assignment of the low skeletal bending modes and the halogen stretching modes follows easily from the undeuterated molecule as can be seen from the line diagram (Fig. 1). The C—C stretching mode in the *trans* form is taken at 1014 cm^{-1} lower than

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that in the *gauche* form at 1028 consistent with the relative intensities of these bands in $\text{ClCH}_2\text{CH}_2\text{Br}$. It appears that the C—C stretching mode in the *trans* form is much more sensitive to deuteration than its counterpart in the *gauche* form in agreement with corresponding observations (5) on $\text{BrCH}_2\text{CH}_2\text{Br}$ and $\text{BrCD}_2\text{CD}_2\text{Br}$.

The CH_2 and CD_2 stretching modes follow quite naturally from the polarization data and require no further discussion.

The low frequency CH_2 modes were assigned by considering the relative frequencies of corresponding modes in the *trans* and *gauche* forms of $\text{ClCH}_2\text{CH}_2\text{Br}$, the CD_2 modes then being assigned in the same relative order. The Teller Redlich product rule (4) was used to assist the assignment of the CH_2 and CD_2 frequencies, the torsional modes being assumed independent of the other vibrations and factorized out from the product ratios where necessary. For the *trans* form the calculated ratio of the torsional frequencies was 0.913 and for the *gauche* form it was 0.988. The final product ratios obtained are quite satisfactory (see Table I).

TABLE I

<i>trans</i> form (C_8)				<i>gauche</i> form (C_1)			
$\text{ClCH}_2\text{CH}_2\text{Br}$		$\text{ClCD}_2\text{CH}_2\text{Br}$		$\text{ClCH}_2\text{CH}_2\text{Br}$		$\text{ClCD}_2\text{CH}_2\text{Br}$	
210 (0)p	δ_{CCBr} (a')	201 (1)p		(248)	δ_{CCBr}	223 (1)p	
248 (6)p	δ_{CCCl} (a')	251 (5)p		385 (3)dp	δ_{CCCl}	374 (1)dp	
629 (6)	ν_{CBr} (a')	635 (4)p		568 (9)p	ν_{CBr}	541 (5)p	
721 (10)p	ν_{CCl} (a')	696 (10)p		665 (6)p	ν_{CCl}	654 (3)p	
1056 (3)dp	ν_{CC} (a')	1014 (3)p		855 (2)dp?	ν_{CH_2}	726 (1)dp?	
1203 (2)p	ν_{CH_2} (a')	940 (1)p		919 (3)p	ν_{CH_2}	860 (1)p	
1282 (4)p	ν_{CH_2} (a')	1233 (3)p		1023 (1)	ν_{CC}	1028 (1)dp	
1439 (2b)dp	δ_{CH_2} (a')	1123 (0)p		1128 (1)dp	ν_{CH_2}	(860) (1)p	
1446 ^a	δ_{CH_2} (a')	1444 (0)p		1189 (2)p	ν_{CH_2}	(1123) (0)	
2964 ^b	ν_{CH} (a')	2966 (4)p		1259 (3)p?	ν_{CH_2}	955 (0)p	
2964 ^b	ν_{CH} (a')	2154 (2)p		1299 (1)	ν_{CH_2}	1248 (1)p	
763 ^a	ν_{CH_2} (a'')	757 (0)dp?		1421 (3b)	δ_{CH_2}	1116 (0)p	
961	ν_{CH_2} (a'')	801 (0)dp?		1428 ^a	δ_{CH_2}	1426 (1)dp	
1111 ^a	ν_{CH_2} (a'')	821 (0)dp?		2964 ^b	ν_{CH_2}	2164 (2)p	
1258 (2)p?	ν_{CH_2} (a'')	1179 (1)dp?		2964 ^b	ν_{CH}	2982 (6)p	
3007 ^b	ν_{CH} (a'')	2257 (2)dp		3007 ^b	ν_{CH}	2241 (1)p	
3007 ^b	ν_{CH} (a'')	3027 (2)dp		3007 ^b	ν_{CH}	(3027) (2)dp	
	$\tau_{\text{obs}} = 0.384$				$\tau_{\text{obs}} = 0.148$		
a' species	$\tau_{\text{calc}} = 0.361^c$				$\tau_{\text{calc}} = 0.136^{c,d}$		
	$\tau_{\text{obs}} = 0.433$						
a'' species	$\tau_{\text{calc}} = 0.408^{c,d}$						
Combination tones							
	calc.	obs.		calc.	obs.		
$2 \times 251 = 502$		491 (0)		$541 - 223 = 318$	313 (0)		
$940 - 696 = 244$		~ 238 (0)p					
$1444 - 757 = 689$		$\sim 668?$ (0)dp		$223 + 374 = 597$	585 (0)		
$1014 + 1123 = 2137$							
$696 + 1444 = 2140$		~ 2137 (0)					
$1123 + 1179 = 2302$		2302 (0)					
$1123 + 1233 = 2356$		2339 (0)					
$2 \times 1179 = 2358$		2357 (0)					
$635 + 2154 = 2789$		2788 (0)dp					
$2 \times 1444 = 2888$		2870 (0)p					

^aInfrared value.

^bTaken from Mizushima, S., *Internal rotation* (Academic Press Inc., New York, 1954, p. 27).

^cThe product ratios were calculated assuming bond lengths $\text{CC} = 1.54$; $\text{CCl} = 1.71$; $\text{CBr} = 1.95$; $\text{CH} = 1.09$ and all angles tetrahedral.

^dContribution from torsional modes factorized out.

() Frequency used twice.

ν , δ , w , t , and τ refer to stretching, bending, wagging, twisting, and rocking, respectively.

Since the halogen stretching vibrations of the *trans* and *gauche* molecules were reasonably separated, the effect of temperature on the intensities of the bands was investigated to determine the energy difference between the two forms. Fig. 2 shows the plot of $\ln(I_{\nu_{\text{C-Cl}}(\text{trans})}/I_{\nu_{\text{C-Br}}(\text{gauche})})$ against $1/T$ for the temperature range -3° to 100°C ., areas of the bands being used for the intensities. The slope of the curve gives the energy difference between the two forms in the liquid as 489 ± 100 cal./mole in reasonable

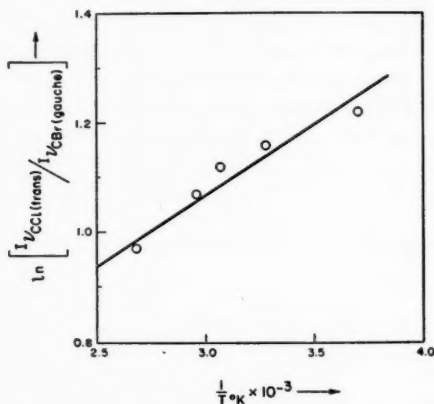


FIG. 2. The plot of $\log (I_{\nu_{\text{C-Cl}}(\text{trans})}/I_{\nu_{\text{C-Br}}(\text{gauche})})$ against $1/T$.

agreement with the value for $\text{ClCH}_2\text{CH}_2\text{Br}$ in the liquid (1) of 395 ± 160 cal./mole obtained from photographic Raman data, but less than the values of 1850 and 1430 cal./mole for the gas (6) as would be expected.

The sample of $\text{ClCD}_2\text{CH}_2\text{Br}$ was obtained through the courtesy of Dr. L. Leitch of these laboratories.

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SOME OBSERVATIONS ON THE HYDROLYSIS OF CYANOGEN CHLORIDE

M. W. LISTER

Cyanogen chloride hydrolyzes slowly to ammonium chloride and carbon dioxide. Douglas and Winkler (1) found the reaction to be first order in cyanogen chloride, with an activation energy of 21 kcal./g-mol., in aqueous solution without added catalyst. Ammonium chloride had virtually no effect on the rate, but potassium nitrate increased

it somewhat. They followed the reaction by silver nitrate titration, which only measures the ammonium chloride formed. Van Cleave *et al.* (8) found the reaction in dioxane to be catalyzed by hydrogen chloride, and the rate to have a very low temperature coefficient. They followed the reaction by filtering off the ammonium chloride. Other cyanides have been found to hydrolyze in somewhat similar fashion (3, 4, 7).

In the present work a method was developed which distinguishes cyanogen chloride from hydrochloric acid or sodium chloride. Using this method it was possible to show that the cyanogen chloride hydrolysis in aqueous solution is catalyzed by hydrochloric acid much as other cyanides are. Sodium chloride, on the other hand, reduced the rate somewhat. The solubility of cyanogen chloride in water was found also to be reduced by sodium chloride, to about the same extent as the rate of reaction.

EXPERIMENTAL METHODS

Cyanogen chloride (from chlorine and sodium cyanide) was purified by distilling it several times through a tube containing phosphorus pentoxide, with rejection of small initial and tail fractions. Finally it was largely frozen, and the remaining liquid poured off. The product was colorless, and boiled at 12.5° C.

Runs were made by sealing weighed amounts of various cyanogen chloride solutions in glass ampoules, and immersing them in a thermostat for known lengths of time. The ampoules were then taken out, cooled in ice, opened, and the contents analyzed by one of the following methods:

(1) When only a small concentration of chloride ions was present, the solution was titrated with silver nitrate to an end point detected by sodium chromate. The solution was then made alkaline (to convert cyanogen chloride to cyanate and chloride ions), acidified with dilute nitric acid, and briefly boiled (to destroy cyanate). After neutralization with calcium carbonate, the silver nitrate titration was continued to a new end point. The difference between the two end points gives the cyanogen chloride.

(2) When much chloride was present, the sample was poured into 0.7 *M* ammonia, containing 0.2 *M* ammonium nitrate, and some lumps of ice; this produces cyanamide. A solution of 0.5 *M* silver nitrate in 2–3 *M* ammonia was run in, thereby precipitating silver cyanamide. The precipitate was filtered on a sintered glass disk, and washed; the filtrate was discarded. The precipitate was stirred with 1 *M* sulphuric acid, and the liquid separated from any undissolved solid, which was washed with a little more sulphuric acid. The sulphuric acid solution, with washings, was boiled for 5–10 minutes. This removed regenerated cyanamide. After the solution had cooled a little, excess calcium carbonate was added. A known amount of standard potassium chloride solution was introduced, in excess of the silver present, and the excess potassium chloride was finally titrated with silver nitrate.

The number of atoms of silver precipitated per molecule of cyanogen chloride was determined by analyzing the same solution by the two methods. This number was expected to be 2, but the average result was nearer to 1.25. Successive analyses gave the results: 1.25, 1.28, 1.23, 1.275, 1.215, 1.20. Hence this method is only accurate to within a few per cent. However, it was used for want of a better one when much hydrochloric acid or sodium chloride was present. It was checked that the two methods gave the same rate constant for the same conditions. Analysis of the silver content of the precipitate gave a result (79.7%) between that calculated for AgHNCN (72.4%) and Ag_2NCN (84.3%); but this is only a rough guide, as a little silver chloride was generally carried

down too. Analytical methods depending on this precipitation, but differing considerably in details, have been described by Hetherington and Braham (2), and by Nanussi (5). Other methods of analysis, by reduction to cyanide, or by conversion of the cyanogen chloride to thiocyanate, were examined, but did not give quantitative results.

RESULTS

Earlier work had established that the reaction is first order in cyanogen chloride; all the present runs confirmed this, and the first order rate constants for various conditions are given below. Without any added acid, the rate constants were:

Run No.	1	2	3	4	5
Temp., ° C.	50	50	40	60	50
Rate constant, hr. ⁻¹	0.0282	0.0277	0.0111	0.0752	0.0279

Runs 1 and 2 were done by method (1), and run 5 by method (2) above, and it can be seen that the rate constants agree. The average rate constant at 50° C. is 0.028 hours⁻¹. This is somewhat lower than that obtained by Douglas and Winkler; but if log (rate constant) is plotted against 1/*T* in the usual way, the present results for 50° C. and 60° C. continue the line of their results at lower temperatures (0°–30° C.). This gives an activation energy a little lower than that obtained by Douglas and Winkler, being close to 20.5 kcal./g-mol.

The effect of adding sodium chloride was as follows:

Run No.	6	7	8
Temp., ° C.	50	50	50
[NaCl] <i>M</i>	3.00	2.03	1.01
Rate constant, hr. ⁻¹	0.0133	0.0185	0.0202

This shows that sodium chloride slows up the reaction. Measurements of the solubility of cyanogen chloride at 30° C. in the same salt solutions showed a diminution by about the same percentage, as compared with the solubility in pure water:

[NaCl] <i>M</i>	0	1.01	2.03	3.00
[CICN] <i>M</i> , satd. at 30° C.:	0.94	0.74	0.53	0.49

If it is assumed, as a rough approximation, that this decrease results from water being attached to the sodium chloride and not free to react, then about 10 molecules of water attached to each sodium chloride (i.e. to the two ions) would account for both sets of changes.

The effect of added hydrochloric acid was as follows:

Run No.	9	10	11	12	13	14	15
Temp., ° C.	50	50	50	50	30	0	0
[HCl] <i>M</i>	1.9	3.05	4.0	6.1	4.2	4.1	6.1
Rate constant, hr. ⁻¹	0.028	0.114	0.55	0.92	0.0895	0.0030	0.0057

This is similar to the results with other cyanides, except that the uncatalyzed reaction is relatively much faster, and it is not until a fairly high concentration of hydrochloric acid is present that the catalysis becomes very effective. The activation energy seems to decrease for the catalyzed reaction, being about 18.3 kcal./g-mol. in roughly 4.1 *M* hydrochloric acid, and (if only runs 13 and 15 are used) about 17.8 kcal./g-mol. in 6.1 *M* acid. It must be admitted that, owing to analytical difficulties, these measurements are not as accurate as in other investigations of cyanide hydrolyses; and the most that can be claimed is that a general similarity of behavior has been demonstrated. Winkler and his co-workers (6, 7) discuss the mode of action of hydrochloric acid in these reactions, and their remarks can also be applied to the hydrolysis of cyanogen chloride.

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GAS PHASE REACTIONS OF PHENYL RADICALS¹

G. W. TAYLOR²

In this note, some observations on the reactions of phenyl radicals in the gas phase at elevated temperatures are described. The work was done in conjunction with a study of the oxidation and pyrolysis of benzene (3). It is shown that dimerization of phenyl radicals probably does not occur to a great extent at 450° C. or higher, but that the radicals readily form substitution products with several aromatic hydrocarbons.

Jaquiss and Szwarc (2) showed that the primary products of the pyrolysis of benzil are phenyl radicals and carbon monoxide. This diketone was, therefore, used as a source of phenyl radicals in the present investigation. Benzil, which was a B.D.H. reagent, was pyrolyzed in sealed Pyrex tubes of diameter 2.5 cm., volume 40 ml., for 40 minutes at 450 to 500° C., both alone and in the presence of benzene, carbon dioxide, anthracene + carbon dioxide, and naphthacene + carbon dioxide. The liquid and solid products were quantitatively analyzed by chromatography on alumina, the developing being done with petroleum ether (b.p. 40–60° C.). Representative gas samples were analyzed by chromatography on a charcoal column after the procedure of Ray (4).

RESULTS

Only a few representative experiments will be described:

(1) 300 mm. of benzil, 450° C. Most of the benzil decomposed to a tarry material which contained no detectable diphenyl.

(2) 300 mm. of benzil + 5 atm. of benzene, 450° C. About 80% of the benzil decomposed. The brown product contained 0.8 M. of diphenyl per mole of benzil decomposed.

(3) 300 mm. of benzil + 20 atm. of benzene, 450° C. The sole non-gaseous product other than a trace of benzaldehyde was diphenyl, 1.2 M. per mole of benzil decomposed. At 500° C., 1.6 M. of diphenyl per mole of benzil decomposed was obtained. Hydrogen was also a product, but only 0.3 M. per mole of benzil decomposed was found. A complete series of runs at 440° C. showed that the mole fraction of benzil decomposed (0.5) was virtually independent of the pressure of benzene over a benzene pressure range of 0 to 30 atm. The pyrolysis of benzene alone at 500° C. yielded about 2% as much diphenyl as in the benzil runs. Benzaldehyde was a trace product at the two temperatures. A

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blank run on 300 mm. of benzaldehyde + 15 atm. of benzene showed that the aldehyde was stable.

(4) 300 mm. of benzil + 20 atm. of carbon dioxide, 450° C. The product was a tar which contained negligible diphenyl.

In view of the recent use of polynuclear aromatic hydrocarbons as radical traps (5), it was considered of interest to study the effect of anthracene and naphthacene on the gas phase reactions of phenyl radicals. In the following experiments, the reactants were diluted with a high pressure of carbon dioxide to maintain the conditions of total pressure comparable with those obtained in the benzene runs at high pressure.

(5) 300 mm. of benzil + 300 mm. of naphthacene + 16 atm. of carbon dioxide, 480° C. The benzil all decomposed. Products found were 5-phenylnaphthacene (0.3 M. per mole of benzil decomposed) and 5,12-phenylenenaphthacene. The compounds, after partial resolution from unidentified hard material on the chromatography column, were identified by their ultraviolet absorption spectra in benzene (1). A careful search in the products revealed no trace of benzene or diphenyl.

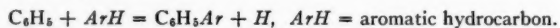
(6) 300 mm. of benzil + 300 mm. of anthracene + 16 atm. of carbon dioxide, 480° C. The column was not capable of completely resolving the products, but the absorption spectra of several fractions revealed the presence of a substantial amount of 9-phenylanthracene. A little yellow compound may have been either 9,12-diphenylanthracene or 1,9-phenyleneanthracene.

Neither anthracene nor naphthacene alone decomposed under the conditions of pyrolysis.

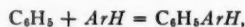
The gaseous products from the side reactions of phenyl radicals were methane, C₂ hydrocarbons, and possibly hydrogen. The principal decomposition product of phenyl was, however, brown tar. In the above experiments, no trace of higher polyphenyls, such as terphenyl, was found under any conditions.

DISCUSSION

The following conclusions can be drawn: The absence of appreciable diphenyl in the products of the pyrolysis of benzil in the presence of carbon dioxide suggests that the dimerization of phenyl radicals is not a major source of diphenyl under the run conditions. The detection of considerable phenyl-substituted polynuclear hydrocarbons in those runs where anthracene or naphthacene were present shows that phenyl radicals can take part in the following reaction:



The absence of benzene in the products shows that phenylation is not a two-stage process,



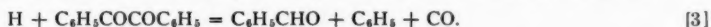
The yields of diphenyl in excess of the moles of benzil decomposed show that phenyl radicals also react with benzene. By analogy with the reaction with polynuclear hydrocarbons, the following reaction is envisaged,



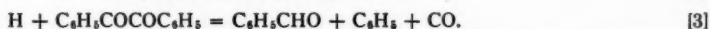
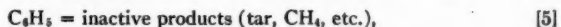
Hydrogen arises from



This sequence requires that the moles of hydrogen be at least equal to the moles of diphenyl in excess of the moles of benzil decomposed. The hydrogen yield is actually considerably less than this, and hence, if reaction [1] occurs, there must be some fate of the hydrogen atom which does not result in the formation of one molecule of hydrogen per atom of hydrogen reacted. Benzaldehyde may arise from a reaction such as



If reaction [1] were the only fate of the phenyl radical in the presence of excess benzene, and if reaction [3] occurred as often as the straight benzil pyrolysis reaction, the yield of diphenyl would be at least 1.5 times the benzil decomposed. Since benzaldehyde is formed only in traces, [3] is not a major process; this means that the yield of diphenyl should actually be in excess of that figure. But, except at 500° C. and very high benzene pressures, this is not the case, and hence the phenyl radical must undergo reaction other than [1]. Another possible fate of phenyl is reaction with benzil itself. But, the mole fraction of benzil decomposed is virtually independent of the pressure of benzene, although the fate of phenyl depends so markedly on the pressure of benzene. This suggests that a reaction between phenyl and benzil does not compete with a reaction between phenyl and benzene. The only alternative fates of phenyl which appear to satisfy these conditions are thermal decomposition and reaction with hydrogen atoms. The complete scheme then becomes:



Reaction [5] accounts for the tarry products in the absence, or presence of small amounts only, of benzene. Reaction [2] will become increasingly important as the temperature is raised, so that the yield of diphenyl will increase, as is, in fact, the case.

At temperatures where [5] and [2] are negligible, this scheme, omitting [3], results in 1 M. of diphenyl per mole of benzil decomposed; under conditions where [2] occurs, the yield of diphenyl is in excess of 1 M. per mole of benzil decomposed, and a chain process involving [1] and [2] will occur. At temperatures much above 500° C., benzene itself decomposes to phenyl radicals complicating the reaction. A chain process involving [1] and [2] is probably the source of diphenyl in the pyrolysis of benzene (3). Reaction [5] will decrease the over-all diphenyl yield.

This work was done while the author was under the supervision of Professor R. G. W. Norrish, F.R.S., in the Department of Physical Chemistry, The University, Cambridge, England. The author would like to express his thanks to Dr. J. H. Purnell for allowing him to use his gas chromatography apparatus.

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A DILUTION VISCOMETER FOR FOAMING LIQUIDS

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In the course of a study of the viscosity of dilute emulsions containing foam-producing emulsifiers, it was necessary to design a capillary viscometer since the existing types were adversely affected by the foaming.

Conventional Ostwald viscometers are inconvenient when viscosity-concentration relationships are studied since each concentration requires a separate filling. Modified forms of Ubbelohde "suspended level" viscometers (1, 2) of suitable design are excellent for dilutions. Neither types, however, could be used for the required purpose since foams were formed and accumulated in the bulbs and thus rendered measurements difficult with the first type and impossible with the second.

The viscometer described in this note proved successful for the purpose and is an Ostwald-type modified to permit (a) control of foam, (b) dilution *in situ*, and (c) measurements at two or more shear rates.

DESCRIPTION

The viscometer is shown diagrammatically in Fig. 1, and consists of the following essential parts:

A	Upper reservoir	F, G	Bulbs
B	Lower reservoir, <i>flat bottomed</i>	H, H ₁	Connecting tubes (2 mm. bore)
C	Ground glass joint (male)	J	Tapered end
D	Ground glass joint (female)	K	Small enlargement
E	Main capillary	L, M, N, O	Reference marks
		P, Q	Side arm

The viscometer bulbs F and G were blown from the connecting tube H. The end J in the reservoir A was tapered on the outside to facilitate the outflow of foam from the tube. A small hole was drilled in C in line with the tube H₁ so that a stopcock was thereby formed to allow flow from tube H₁ into the reservoir B.

OPERATION

A suitable volume of the foam-producing liquid is introduced into the upper reservoir A. The stopcock is opened and by application of *gentle* suction the liquid is transferred through H₁ to the lower reservoir B by flowing down the side arm P. This operation is easily mastered with practice. If foam accumulates in the side arm P or upper portion of B, it can be broken down by judicious application and release of suction through C with the stopcock closed.

When a sufficient volume of the liquid has been transferred to B, the stopcock is closed. By application of suction through the tube Q, the liquid is drawn through the capillary and the bulbs until it overflows at J. Any foam present is carried through J and trapped in the reservoir A. Gentle suction is continued until the meniscus stands at the mark O. The suction is stopped and the liquid flows back into the reservoir B. By timing the fall of the meniscus between the marks L, M, and N, viscosities corresponding to different mean rates of shear are measured in the usual way.

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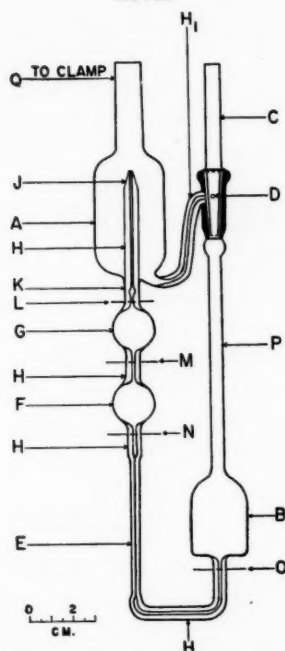


FIG. 1. Sketch of viscometer (approximately to scale).

The dimensions of the viscometer are so chosen that while the liquid meniscus falls from the end J to the mark L on the left side, the liquid in the right side rises from the mark O to the flat bottom of the reservoir B and forms a shallow layer. In the model used, the diameter of B was 14 times that of the connecting tubes. Any variation of initial head resulting from errors in adjusting to the mark O is thereby made negligible. The initial head and the volume of the liquid flowing are therefore independent of the total volume of the liquid in the viscometer.

Table I shows typical measurements on a foaming liquid. After each run the viscometer was adjusted by transferring liquid from the reservoir A to B.

TABLE I
EFFLUX TIMES OF AQUEOUS GLYCERIN CONTAINING
1% POLYOXYETHYLENE SORBITAN MONOLAUATE
(TWEEN 20)

Runs	Time in seconds	
	Bulb 1	Bulb 2
1	74.1	110.6
	74.2	110.7
	74.2	110.7
2	74.2	110.8
	74.1	110.7
	74.2	110.7
3	74.3	110.7
	74.1	110.8
	74.2	110.8

To dilute, a known volume of diluent is poured into the upper reservoir A. The liquid is sucked completely to the lower reservoir B where it is mixed with the rest of the solution. The mixture is then sucked up to the reservoir A and the cycle is repeated two to four times until the mixture is homogeneous.

This viscometer has been used to determine the relative viscosity of foaming emulsions to a precision of 0.2% or better. These results will be published separately.

It should be noted here that the kinetic energy correction, determined in the usual way with glycerin solutions, was positive, i.e. of the same sign usually found for an Ostwald viscometer. The maximum correction necessary for the bulbs was about 0.2% for the range studied.

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2. SCHURZ, J. and IMMERGUT, E. H. *J. Polymer Sci.* **9**, 279 (1942).

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